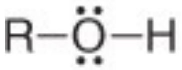
# Alcohols, Ethers and Epoxides

Chapter 17-18

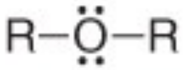
Organic Chemistry, *8th Edition*

John McMurry

# Introduction—Structure and Bonding



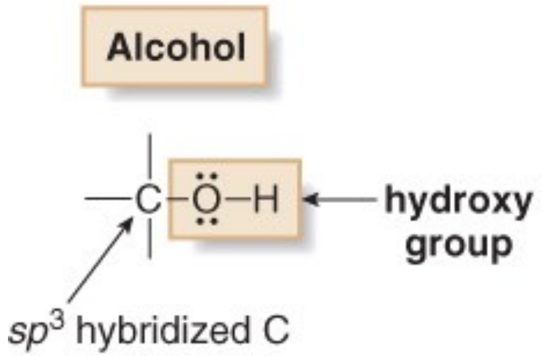
alcohol

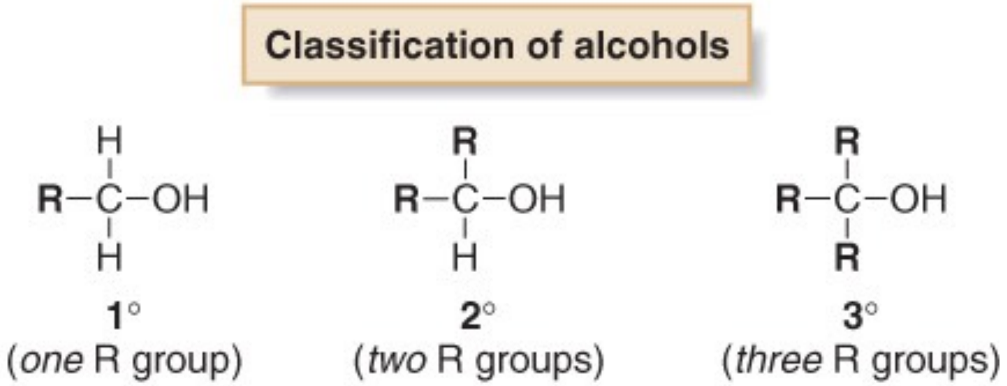


ether

epoxide

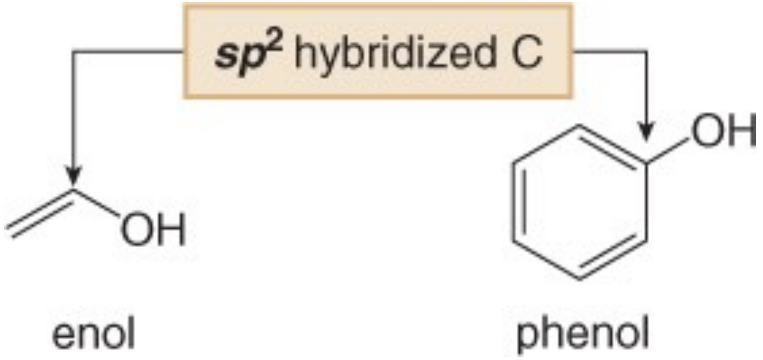
Alcohols contain a hydroxy group (OH) bonded to an sp3 hybridized carbon.



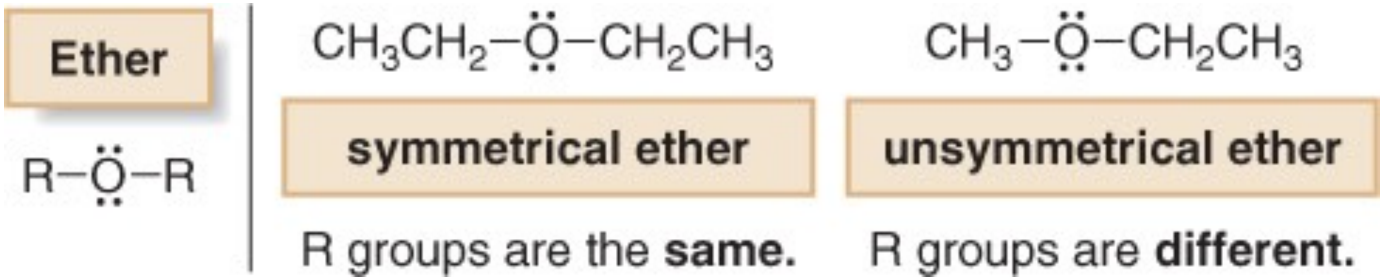


# Introduction—Structure and Bonding

enols and phenols—undergo different reactions than alcohols.



Ethers have two hydrocarbon groups groups bonded to an oxygen atom.



$R-\ddot{\underset{..}{O}}-R$

$CH_3CH_2-\ddot{\underset{..}{O}}-CH_2CH_3$

**symmetrical ether**

R groups are the **same.**

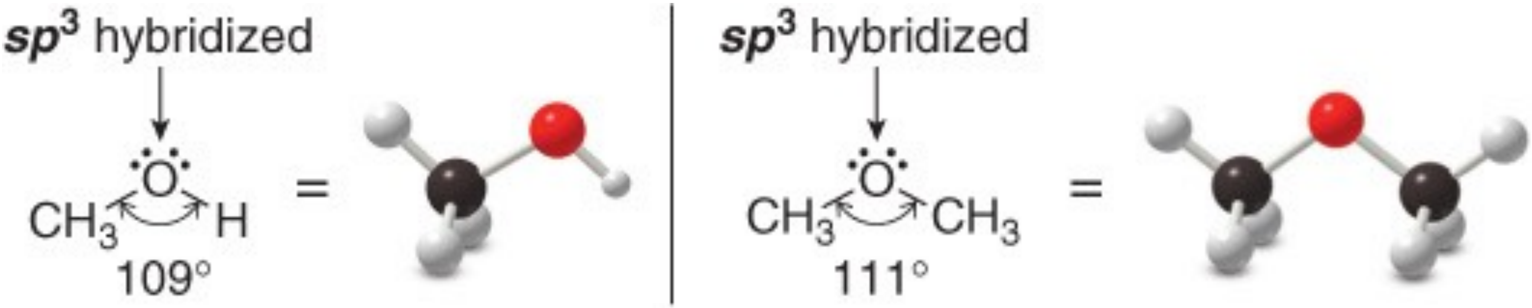
$CH_3-\ddot{\underset{..}{O}}-CH_2CH_3$

**unsymmetrical ether**

R groups are **different.**

# Introduction—Structure and Bonding

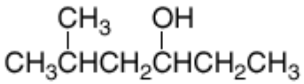
- The oxygen atom in alcohols, ethers and epoxides is *sp*$^3$ hybridized. Alcohols and ethers have a bent shape like that in $H_2O$.
- The bond angle around the O atom in an alcohol or ether is similar to the tetrahedral bond angle of 109.5°.
- Because the O atom is much more electronegative than carbon or hydrogen, the C—O and O—H bonds are all polar.



# Nomenclature of Alcohols

## **How To** Name an Alcohol Using the IUPAC System

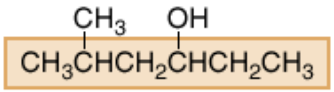
**Example** Give the IUPAC name of the following alcohol:



$$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{OH}{|}}{C}HCH_2CH_3$$

---

**Step [1]** Find the longest carbon chain containing the carbon bonded to the OH group.



$$\boxed{CH_3\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{OH}{|}}{C}HCH_2CH_3}$$

**6** C's in the longest chain

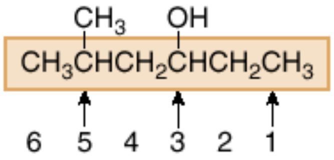
**6 C's** ⟶ **hexane** ⟶ **hexan*ol***

- Change the ***-e*** ending of the parent alkane to the suffix ***-ol.***

---

**Step [2]** Number the carbon chain to give the OH group the lower number, and apply all other rules of nomenclature.

a. **Number** the chain.

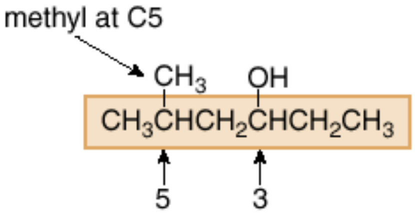


$$\boxed{CH_3\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{OH}{|}}{C}HCH_2CH_3}$$

- Number the chain to put the OH group at C3, not C4.

3-hexanol

b. **Name** and **number** the substituents.

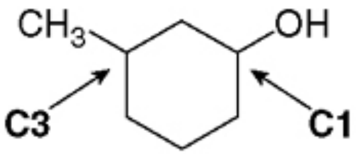


$$\boxed{CH_3\overset{\overset{CH_3}{|}}{C}HCH_2\overset{\overset{OH}{|}}{C}HCH_2CH_3}$$

**Answer: 5-methyl-3-hexanol**

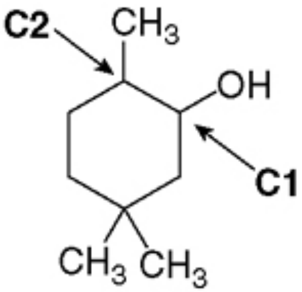
# Nomenclature of Alcohols

- When an OH group is bonded to a ring, the ring is numbered beginning with the OH group. .



**3-methylcyclohexanol**

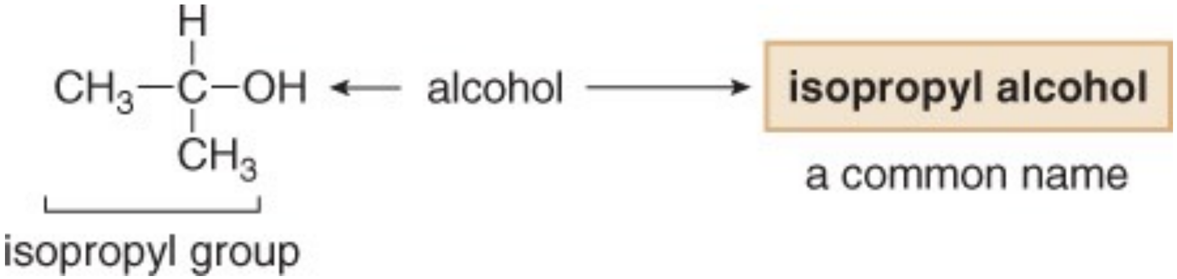
The OH group is at C1; the second substituent ($CH_3$) gets the lower number.



**2,5,5-trimethylcyclohexanol**

The OH group is at C1; the second substituent ($CH_3$) gets the lower number.

- Common names are often used for simple alcohols.



$$CH_3-\overset{\displaystyle H}{\underset{\displaystyle CH_3}{C}}-OH$$

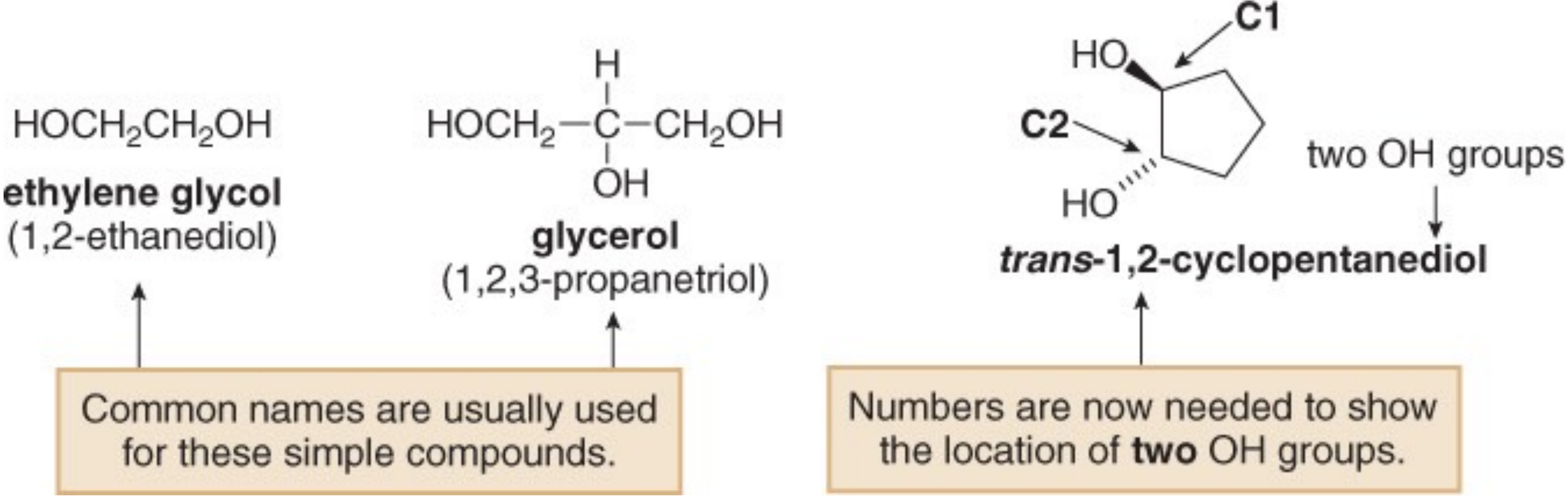
**isopropyl alcohol**

a common name

isopropyl group

# Nomenclature of Alcohols

- Compounds with two hydroxy groups are called diols or glycols. Compounds with three hydroxy groups are called triols and so forth.



$HOCH_2CH_2OH$

**ethylene glycol**
(1,2-ethanediol)

$HOCH_2-\overset{\displaystyle H}{\underset{\displaystyle OH}{C}}-CH_2OH$

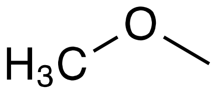
**glycerol**
(1,2,3-propanetriol)

Common names are usually used for these simple compounds.

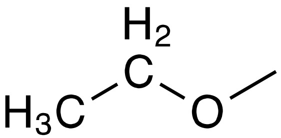
***trans*-1,2-cyclopentanediol**

Numbers are now needed to show the location of **two** OH groups.

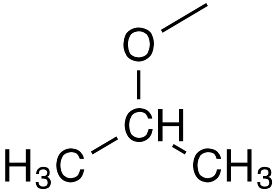
# Nomenclature of Alcohols



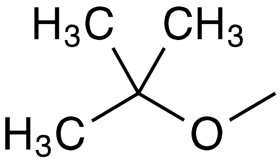
Methoxy



ethoxy



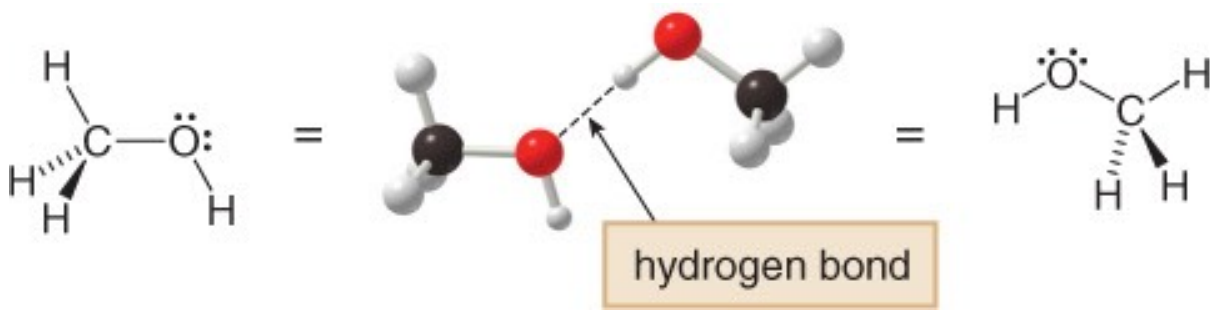
2-propoxy
isopropoxy



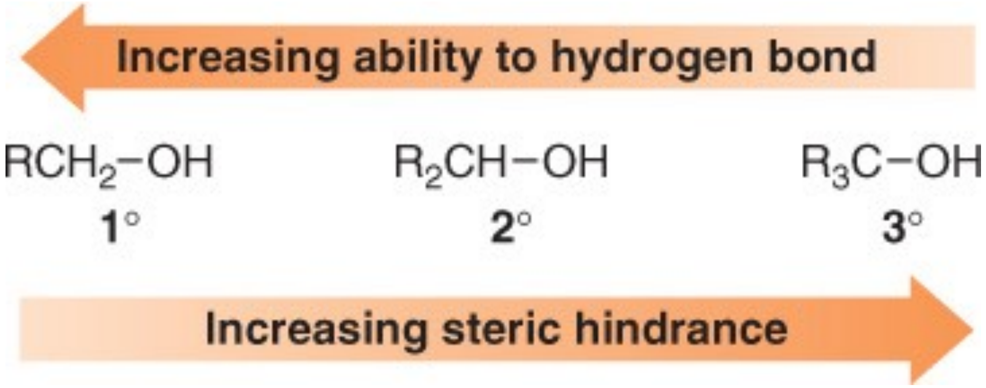
2-methyl-2-propoxy
terbutoxy

# Physical Properties

- dipole-dipole interactions.
- intermolecular hydrogen bonding. Alcohols are more polar than ethers and epoxides.



- Steric factors affect hydrogen bonding.



Increasing ability to hydrogen bond

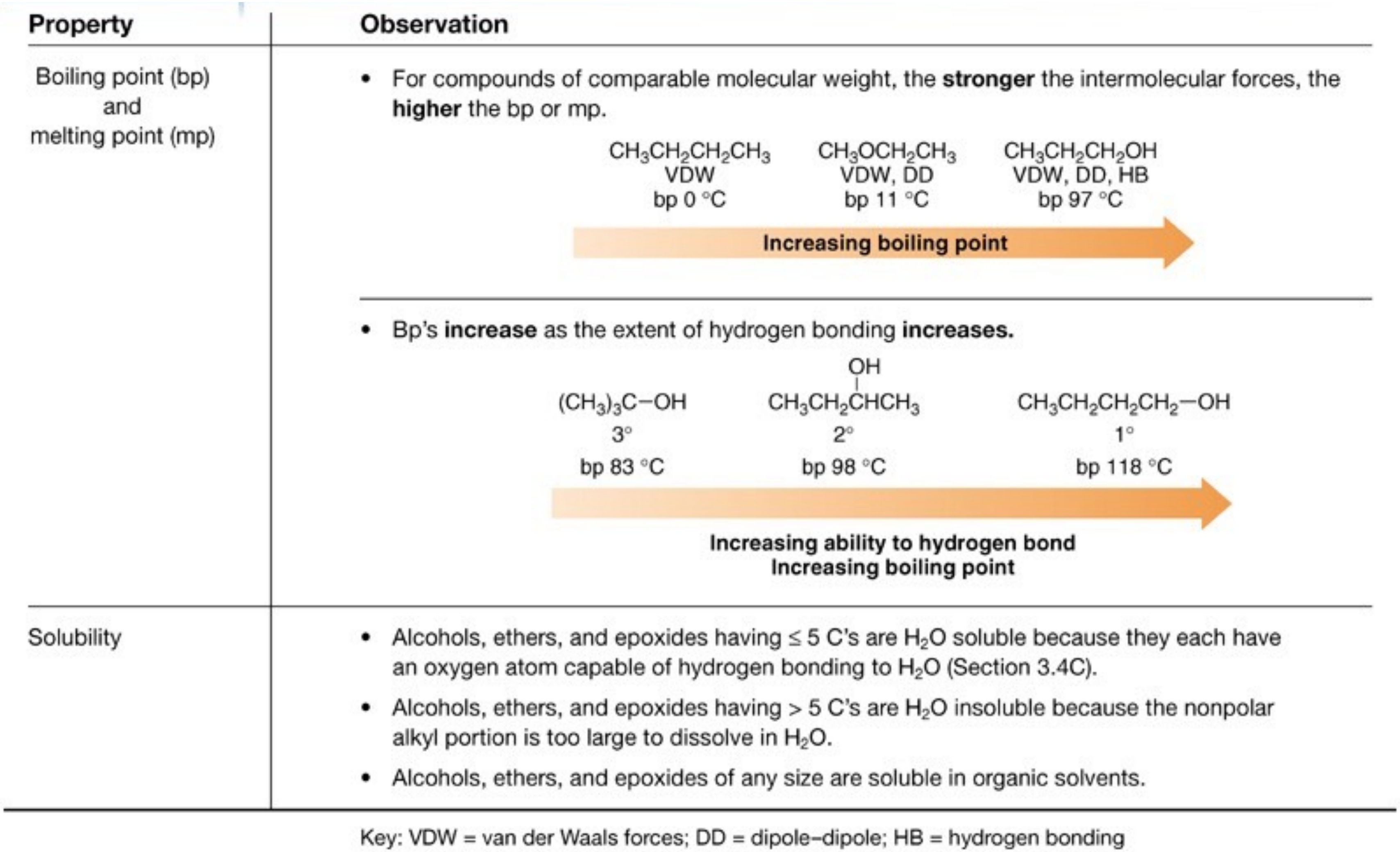
$RCH_2-OH$ 1°

$R_2CH-OH$ 2°

$R_3C-OH$ 3°

Increasing steric hindrance

# Physical Properties



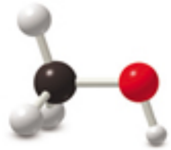
| Property | Observation |
|---|---|
| Boiling point (bp) and melting point (mp) | • For compounds of comparable molecular weight, the **stronger** the intermolecular forces, the **higher** the bp or mp.<br>$CH_3CH_2CH_2CH_3$ VDW bp 0 °C<br>$CH_3OCH_2CH_3$ VDW, DD bp 11 °C<br>$CH_3CH_2CH_2OH$ VDW, DD, HB bp 97 °C<br>**Increasing boiling point** |
|  | • Bp's **increase** as the extent of hydrogen bonding **increases.**<br>$(CH_3)_3C{-}OH$ 3° bp 83 °C<br>$CH_3CH_2\overset{OH}{\overset{\vert}{C}}HCH_3$ 2° bp 98 °C<br>$CH_3CH_2CH_2CH_2{-}OH$ 1° bp 118 °C<br>**Increasing ability to hydrogen bond**<br>**Increasing boiling point** |
| Solubility | • Alcohols, ethers, and epoxides having ≤ 5 C's are $H_2O$ soluble because they each have an oxygen atom capable of hydrogen bonding to $H_2O$ (Section 3.4C).<br>• Alcohols, ethers, and epoxides having > 5 C's are $H_2O$ insoluble because the nonpolar alkyl portion is too large to dissolve in $H_2O$.<br>• Alcohols, ethers, and epoxides of any size are soluble in organic solvents. |

Key: VDW = van der Waals forces; DD = dipole–dipole; HB = hydrogen bonding

# Interesting Alcohols

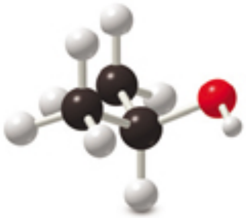
- Ethanol is the alcohol in red wine, obtained by the fermentation of grapes.

# Interesting Alcohols



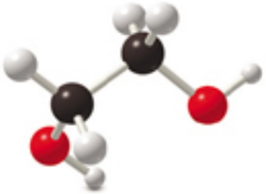
$CH_3OH$

- **Methanol ($CH_3OH$)** is also called wood alcohol, because it can be obtained by heating wood at high temperatures in the absence of air. Methanol is extremely toxic because of the oxidation products formed when it is metabolized in the liver (Section 12.14). Ingestion of as little as 15 mL causes blindness, and 100 mL causes death.



$(CH_3)_2CHOH$

- **2-Propanol [$(CH_3)_2CHOH$]** is the major component of rubbing alcohol. When rubbed on the skin it evaporates readily, producing a pleasant cooling sensation. Because it has weak antibacterial properties, 2-propanol is used to clean skin before minor surgery and to sterilize medical instruments.

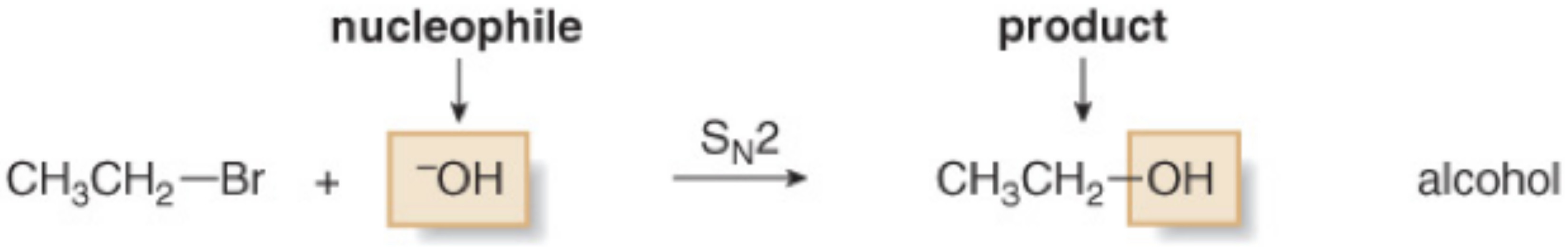


$HOCH_2CH_2OH$

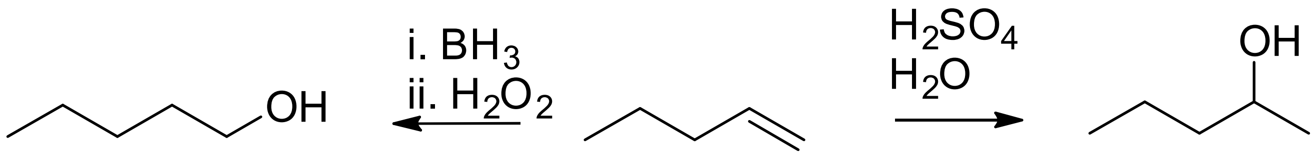
- **Ethylene glycol ($HOCH_2CH_2OH$)** is the major component of antifreeze. It is readily prepared from ethylene oxide by reactions discussed in Section 9.15. It is sweet tasting but toxic.

# Preparation of Alcohols

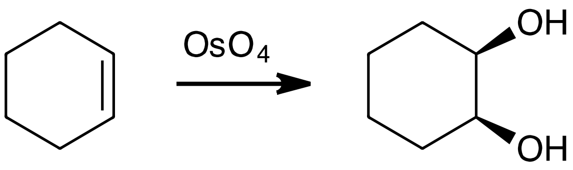
- From alkyl halides



- Hydration/hydroboration of alkenes

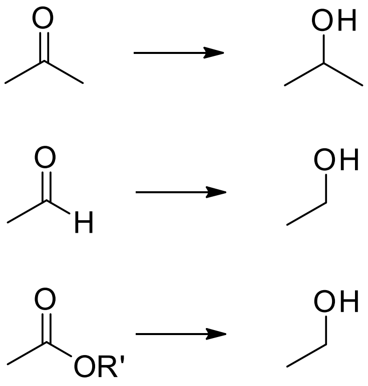


- Dihydroxylation of alkenes



# Preparation of Alcohols

- Reduction of carbonyl compounds

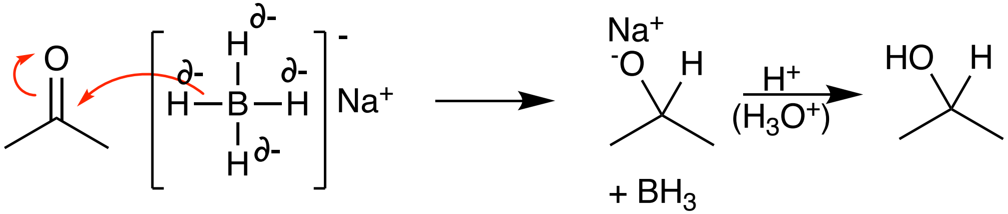


secondary alcohol

primary alcohol

| | |
|---|---|
| $H_2/Pd$ | reduces also C=C |
| $NaBH_4$, $LiAlH_4$ | selective for C=O |

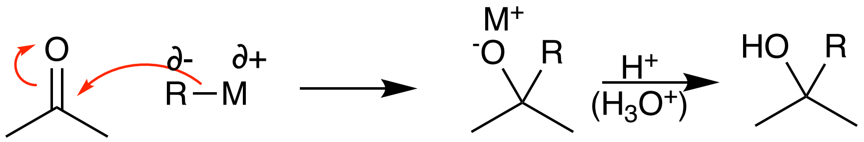
Mechanism: nucleophilic addition to the C=O bond



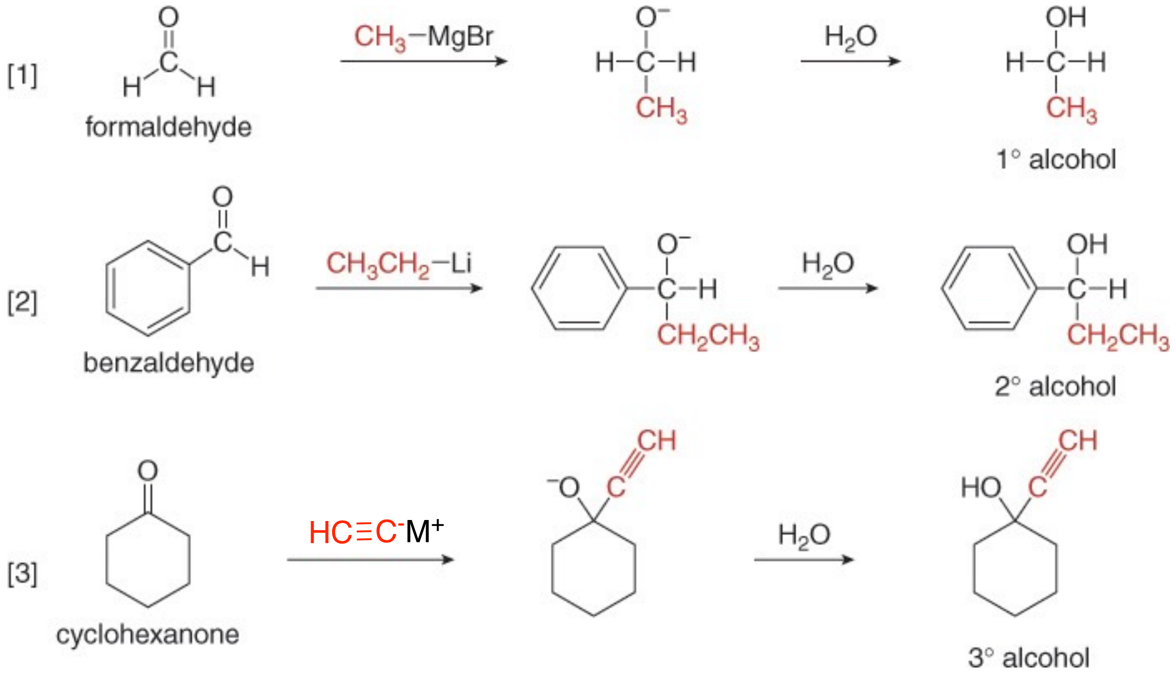
H is transferred as $[H^-]$

# Reaction of carbonyl compounds with organometallic reagents

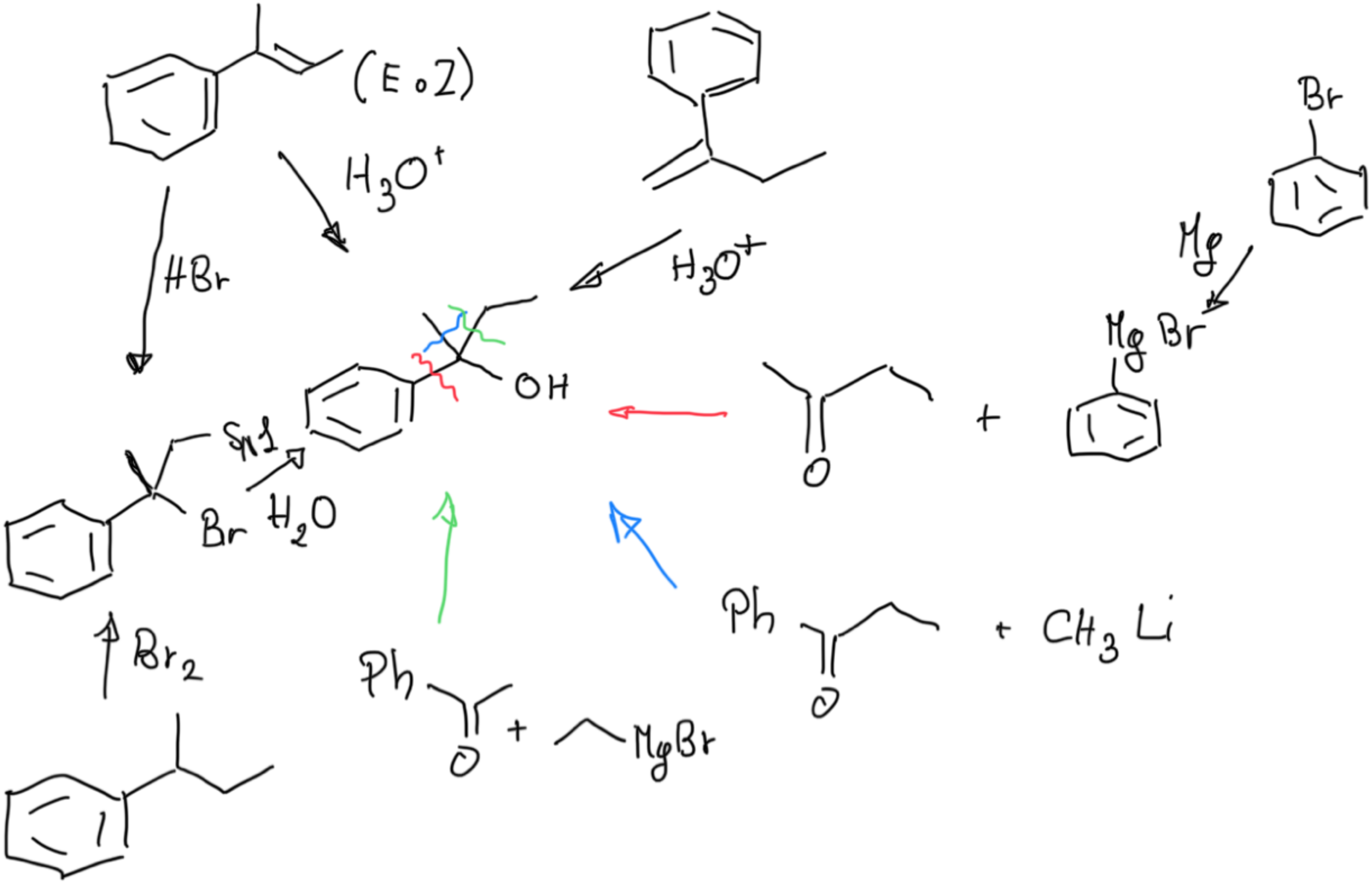
Mechanism: nucleophilic addition to the C=O bond



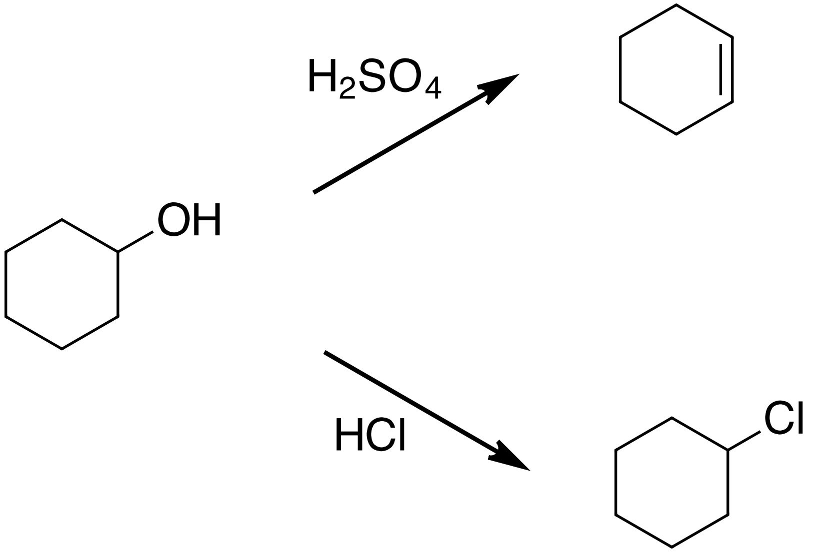
R is transferred as $[R^-]$



# Synthesis of Alcohols



# Reactions of Alcohols
# OH as Leaving Group

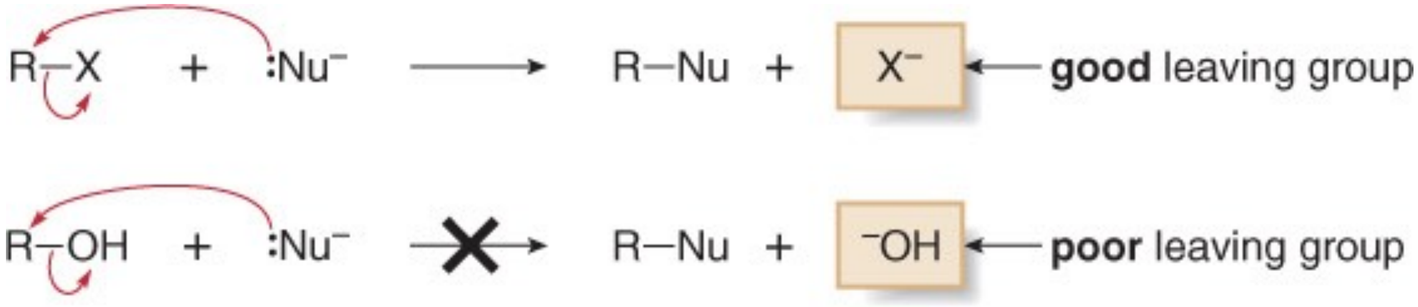


Elimination

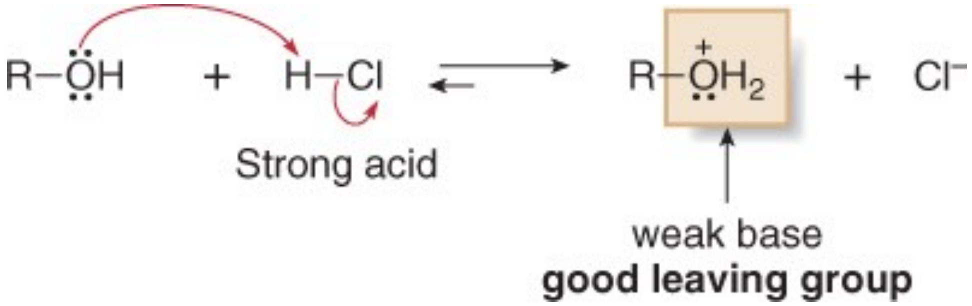
Substitution

# Reactions of Alcohols
# OH as Leaving Group

- The OH group in alcohols is a very poor leaving group.

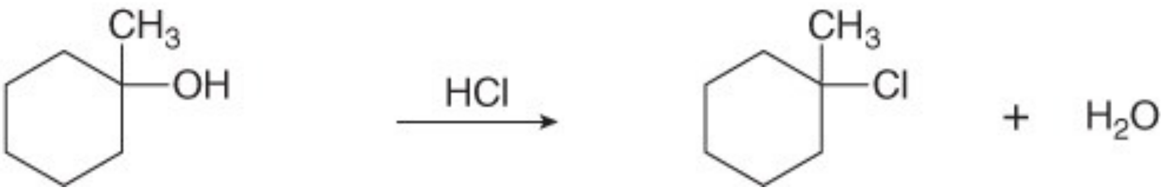


- By using acid, -OH can be converted into $–OH_2^+$, a good leaving group.

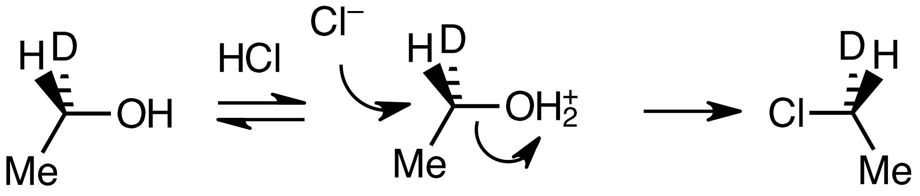


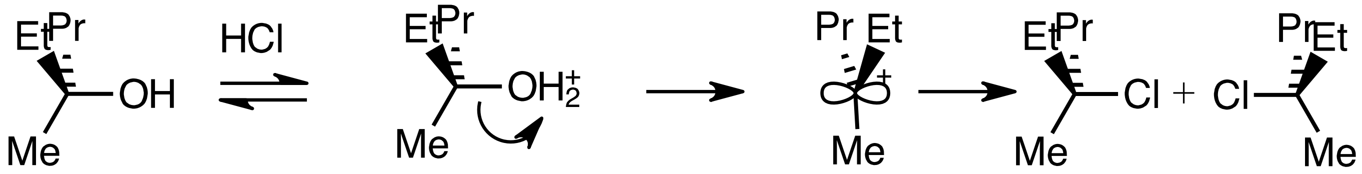
# Conversion of Alcohols to Alkyl Halides

- The reaction of alcohols with HX (X = Cl, Br, I) is a general method to prepare alkyl halides.



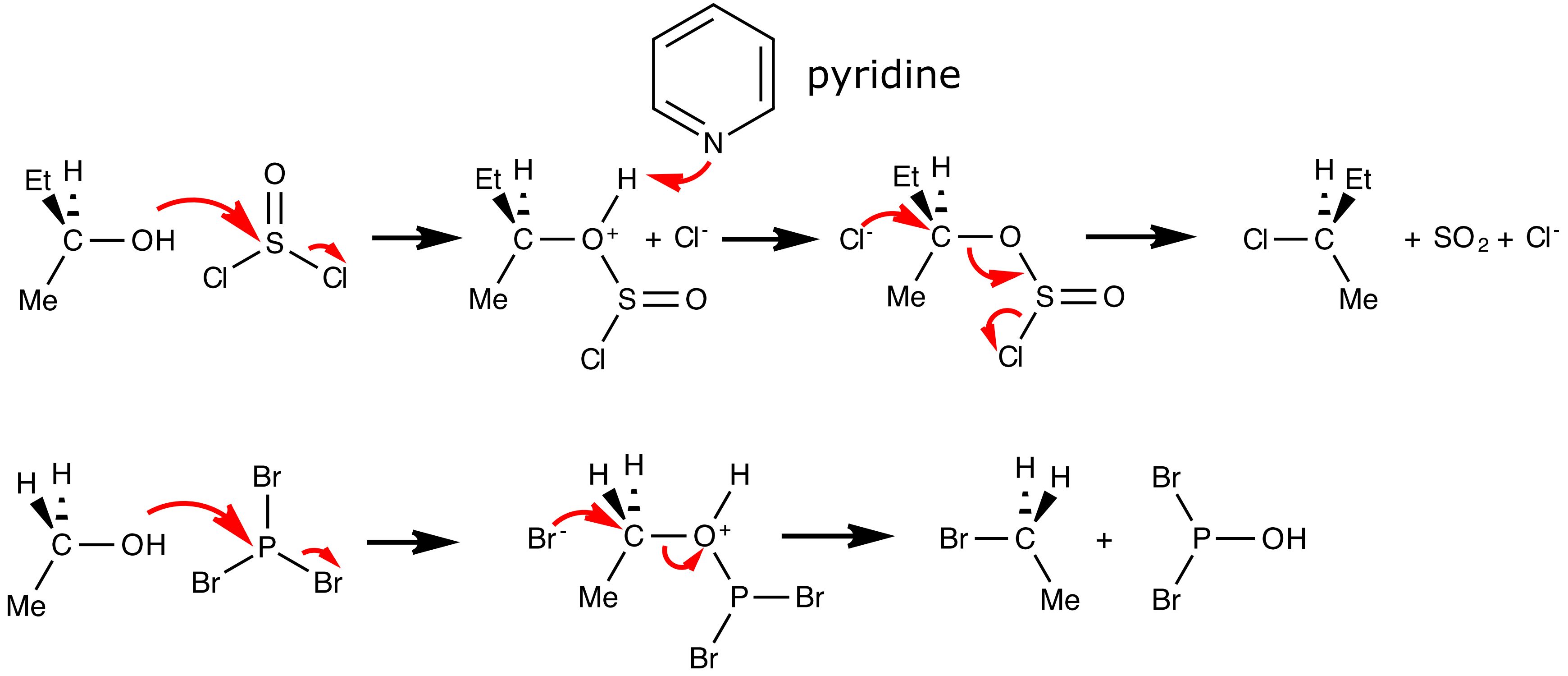
- Mechanism:
    - 1ry alcohols: SN2
    - 2ry alcohols: SN2 or SN1
    - 3ry alcohols: SN1



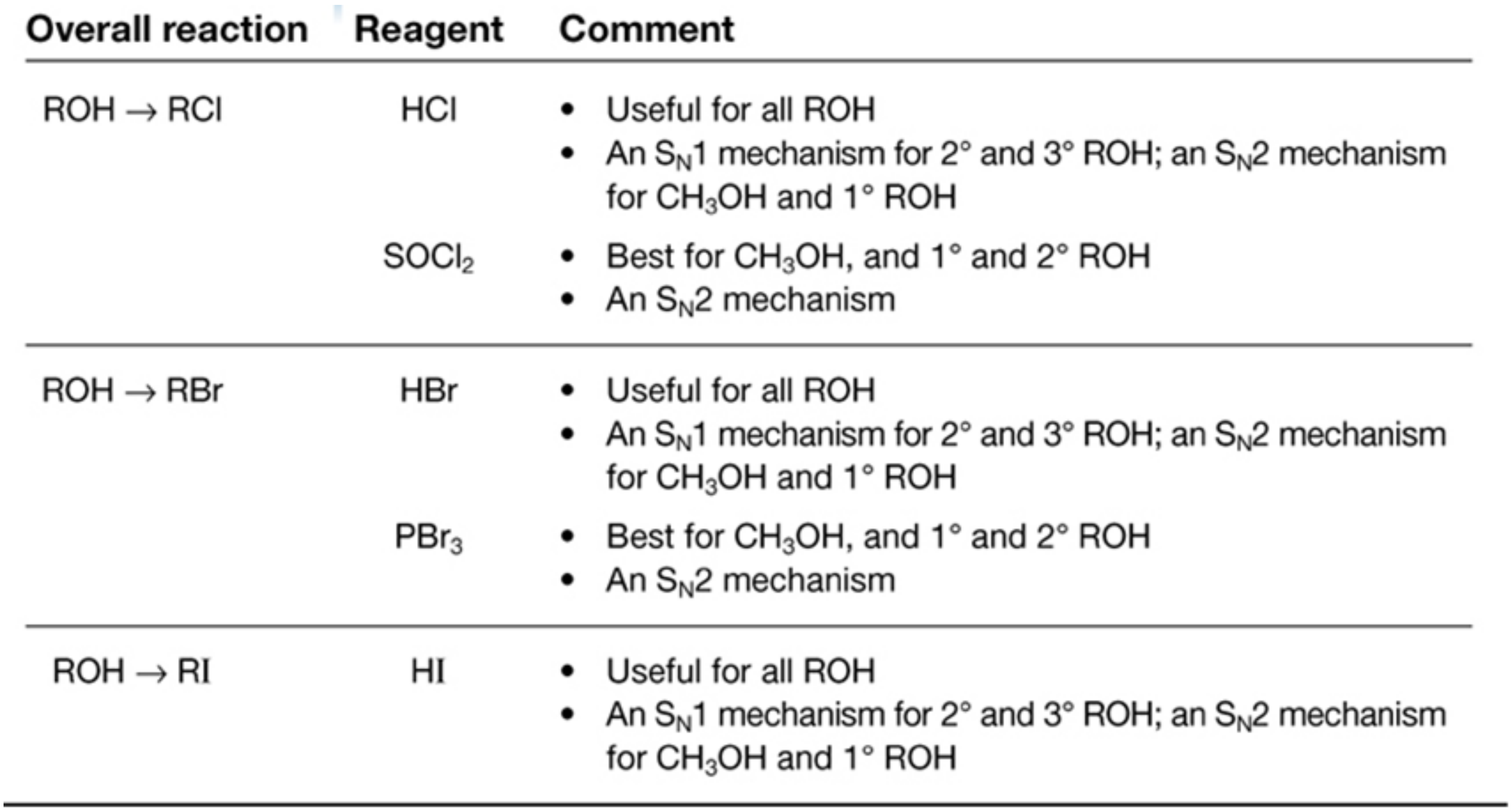


# Conversion of Alcohols to Alkyl Halides with SOCl2 and PBr3

- Primary and secondary alcohols can be converted to alkyl halides using $SOCl_2$ (thionyl chloride) and $PBr_3$ (phosphorus tribromide)



# Conversion of Alcohols to Alkyl Halides

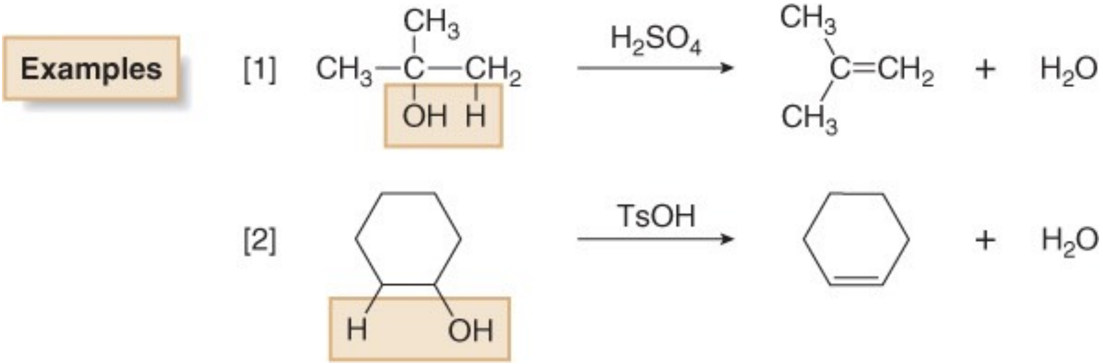


| Overall reaction | Reagent | Comment |
|---|---|---|
| ROH → RCl | HCl | • Useful for all ROH<br>• An $S_N1$ mechanism for 2° and 3° ROH; an $S_N2$ mechanism for $CH_3OH$ and 1° ROH |
| | $SOCl_2$ | • Best for $CH_3OH$, and 1° and 2° ROH<br>• An $S_N2$ mechanism |
| ROH → RBr | HBr | • Useful for all ROH<br>• An $S_N1$ mechanism for 2° and 3° ROH; an $S_N2$ mechanism for $CH_3OH$ and 1° ROH |
| | $PBr_3$ | • Best for $CH_3OH$, and 1° and 2° ROH<br>• An $S_N2$ mechanism |
| ROH → RI | HI | • Useful for all ROH<br>• An $S_N1$ mechanism for 2° and 3° ROH; an $S_N2$ mechanism for $CH_3OH$ and 1° ROH |

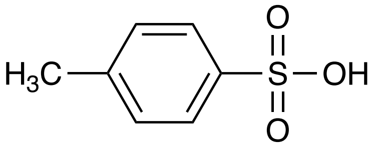
# Reactions of Alcohols—Dehydration

- Dehydration, like dehydrohalogenation, is a β-elimination reaction in which the elements of OH and H are removed from the α and β carbon atoms respectively.

- Typical acids used for alcohol dehydration are $H_2SO_4$ or *p*-toluenesulfonic acid (TsOH).



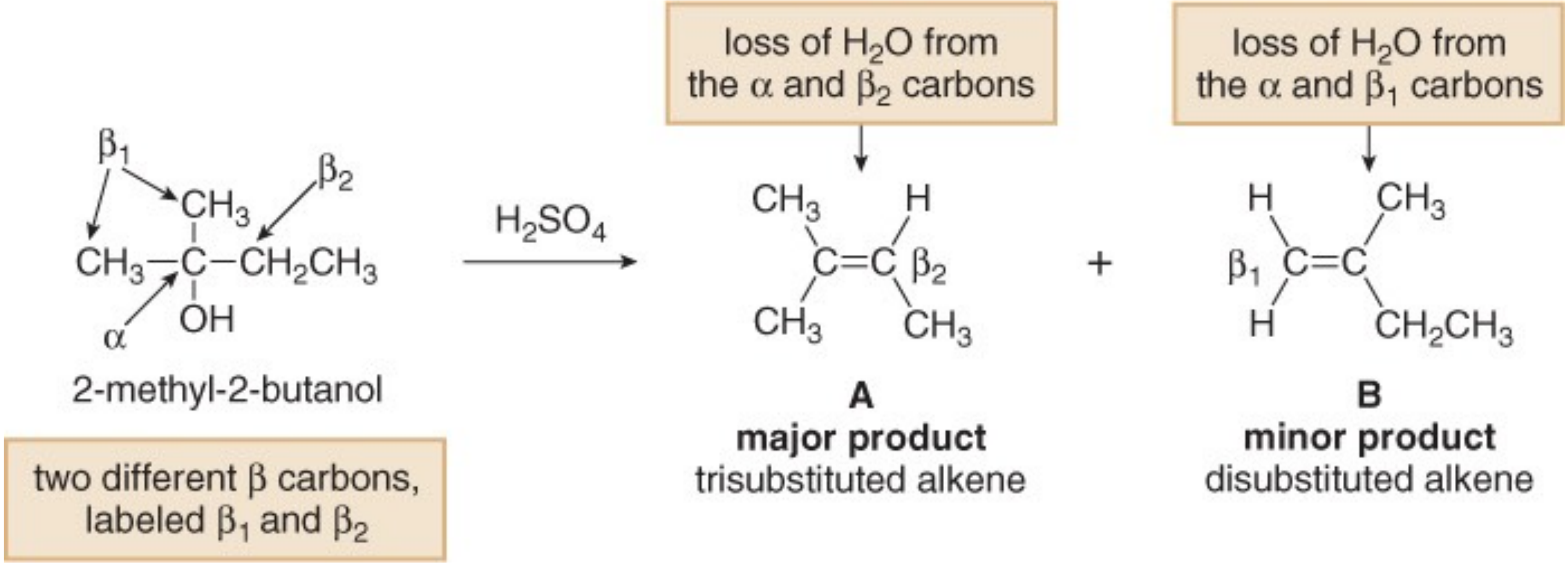
TsOH:



a strong organic acid with a non-nucleophilic anion

# Reactions of Alcohols—Dehydration

- Dehydration is regioselective and follows the Zaitsev rule, giving the more substituted alcohol.



2-methyl-2-butanol

two different β carbons, labeled $\beta_1$ and $\beta_2$

loss of $H_2O$ from the α and $\beta_2$ carbons

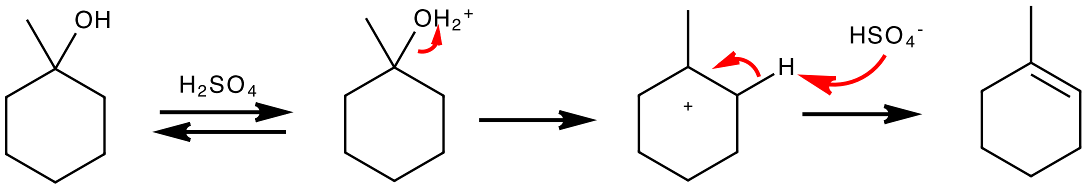
**A**
**major product**
trisubstituted alkene

loss of $H_2O$ from the α and $\beta_1$ carbons

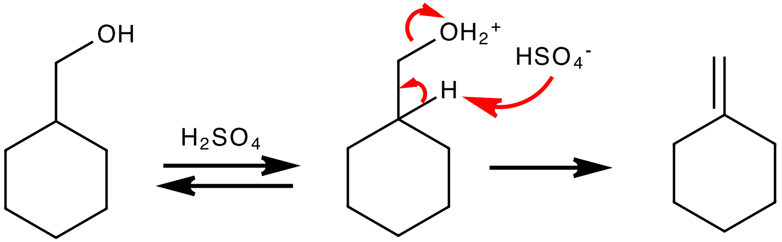
**B**
**minor product**
disubstituted alkene

# Reactions of Alcohols—Dehydration

- Tertiary alcohols react by an E1 mechanism.

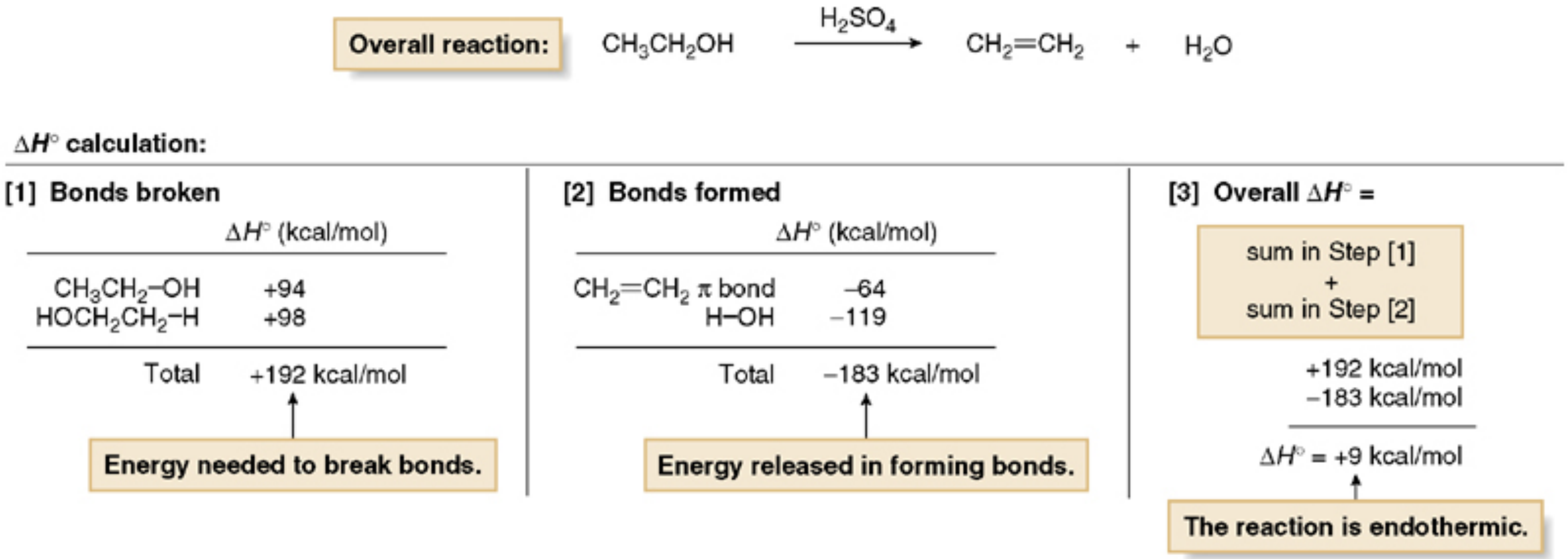


- 1ry alcohols undergo dehydration following an E2 mechanism.



# Reactions of Alcohols—Dehydration

- Although entropy favours product formation in dehydration (i.e., one molecule of reactant forms two molecules of product), enthalpy does not, since the σ bonds broken in the reactant are stronger than the σ and π bonds formed in the products.



**Overall reaction:** $CH_3CH_2OH \xrightarrow{H_2SO_4} CH_2{=}CH_2 + H_2O$

**ΔH° calculation:**

**[1] Bonds broken**

| | ΔH° (kcal/mol) |
|---|---|
| $CH_3CH_2{-}OH$ | +94 |
| $HOCH_2CH_2{-}H$ | +98 |
| Total | +192 kcal/mol |

**Energy needed to break bonds.**

**[2] Bonds formed**

| | ΔH° (kcal/mol) |
|---|---|
| $CH_2{=}CH_2$ π bond | −64 |
| H−OH | −119 |
| Total | −183 kcal/mol |

**Energy released in forming bonds.**

**[3] Overall ΔH° =**

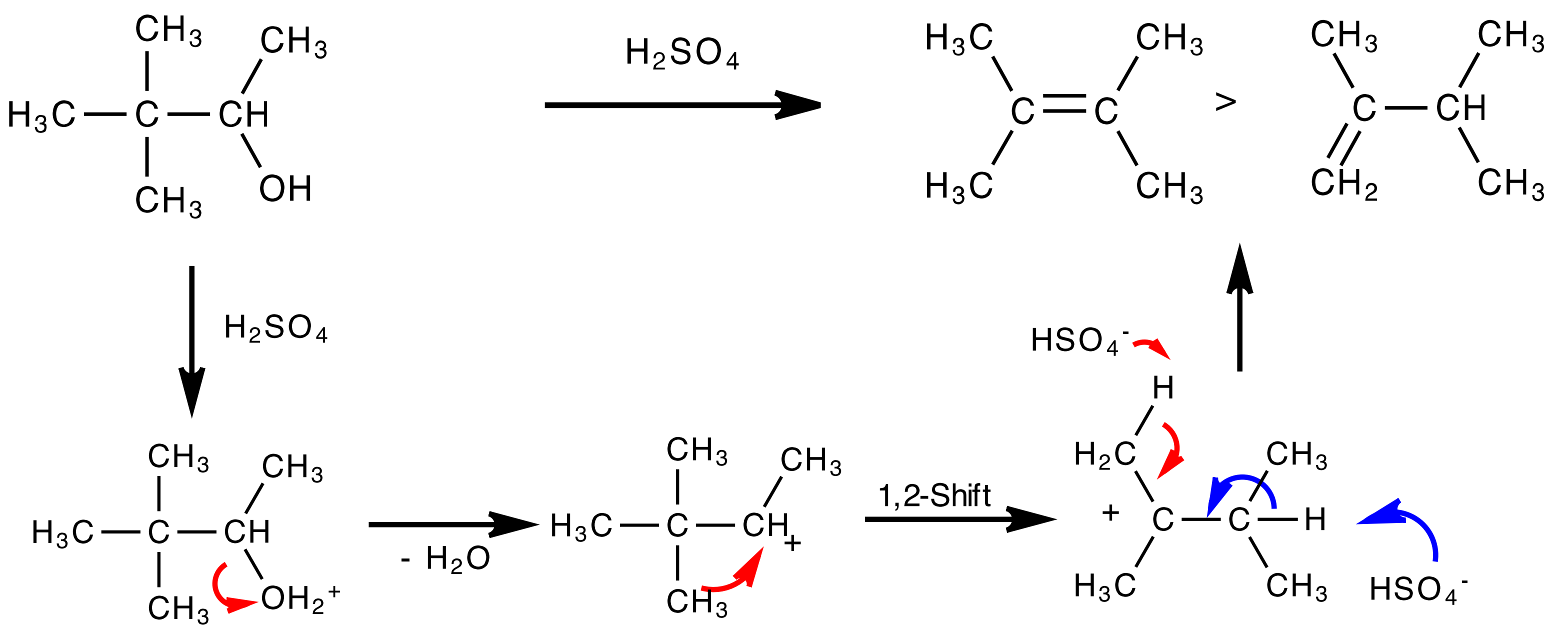
sum in Step [1]
+
sum in Step [2]

+192 kcal/mol
−183 kcal/mol

ΔH° = +9 kcal/mol

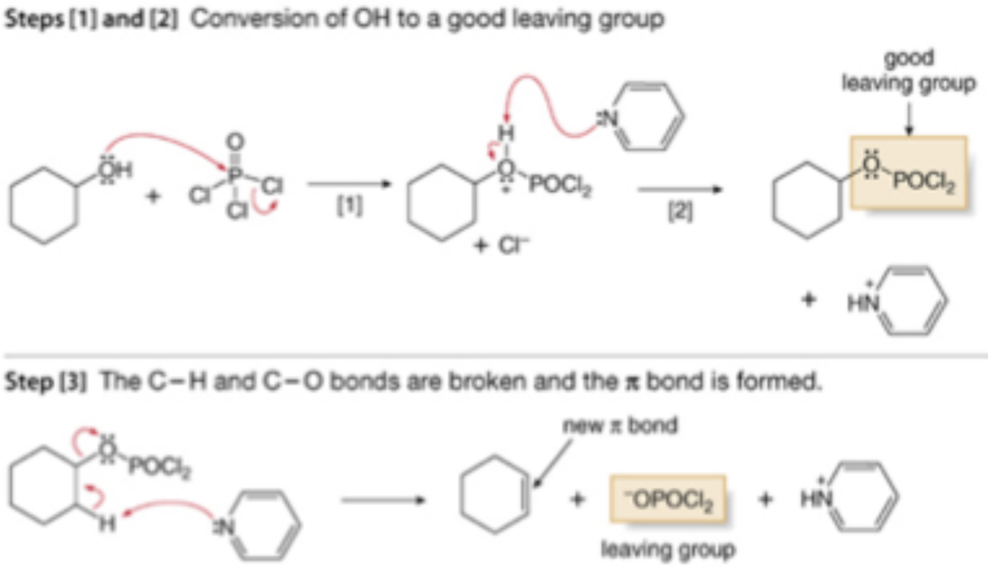
**The reaction is endothermic.**

# Carbocation Rearrangements



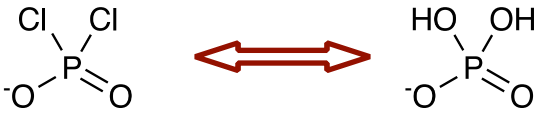
# Dehydration of Alcohols with POCl3 and Pyridine

- Some organic compounds decompose in the presence of strong acid, so other methods have been developed to convert alcohols to alkenes.



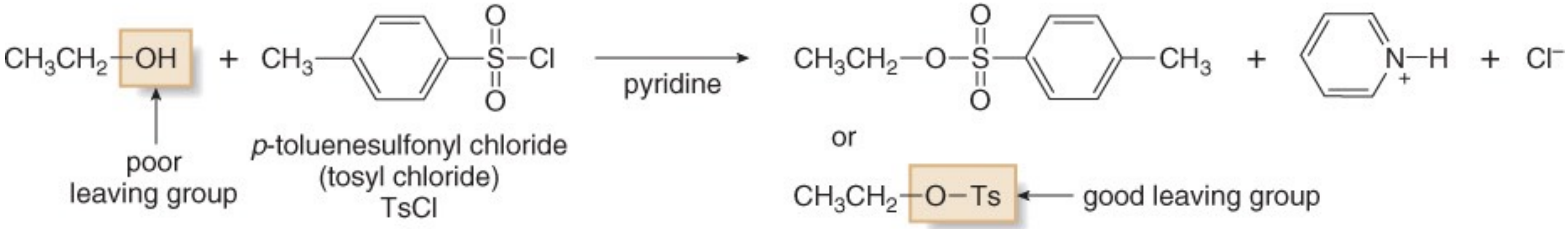
**Steps [1] and [2]** Conversion of OH to a good leaving group

**Step [3]** The C–H and C–O bonds are broken and the π bond is formed.

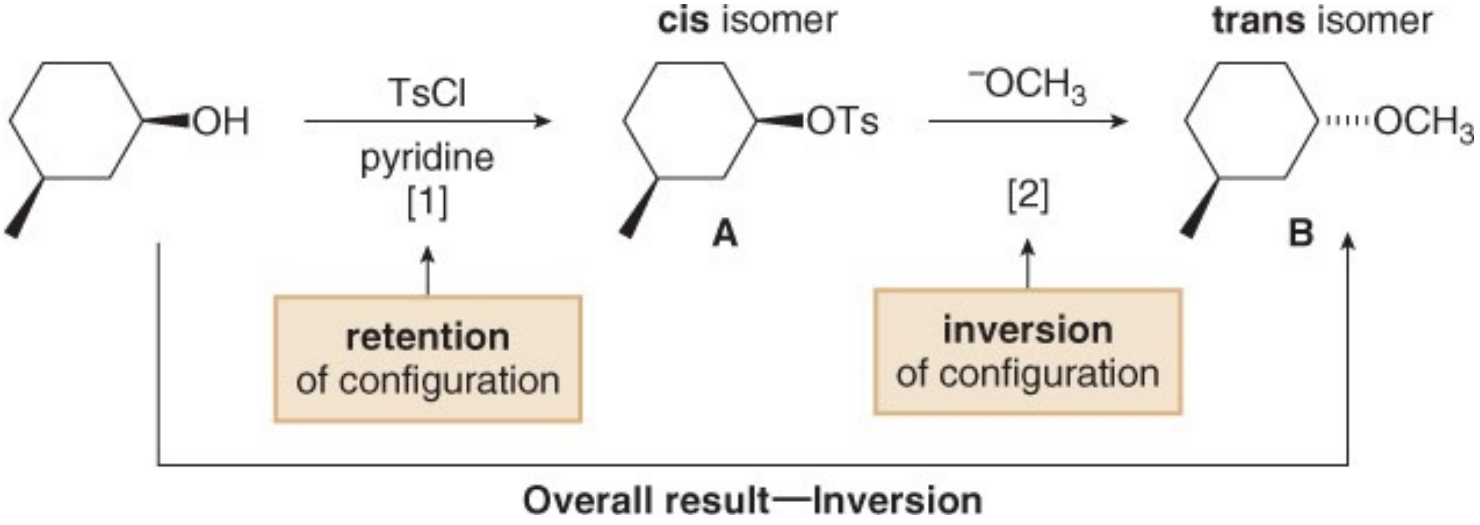


similar structure and stability

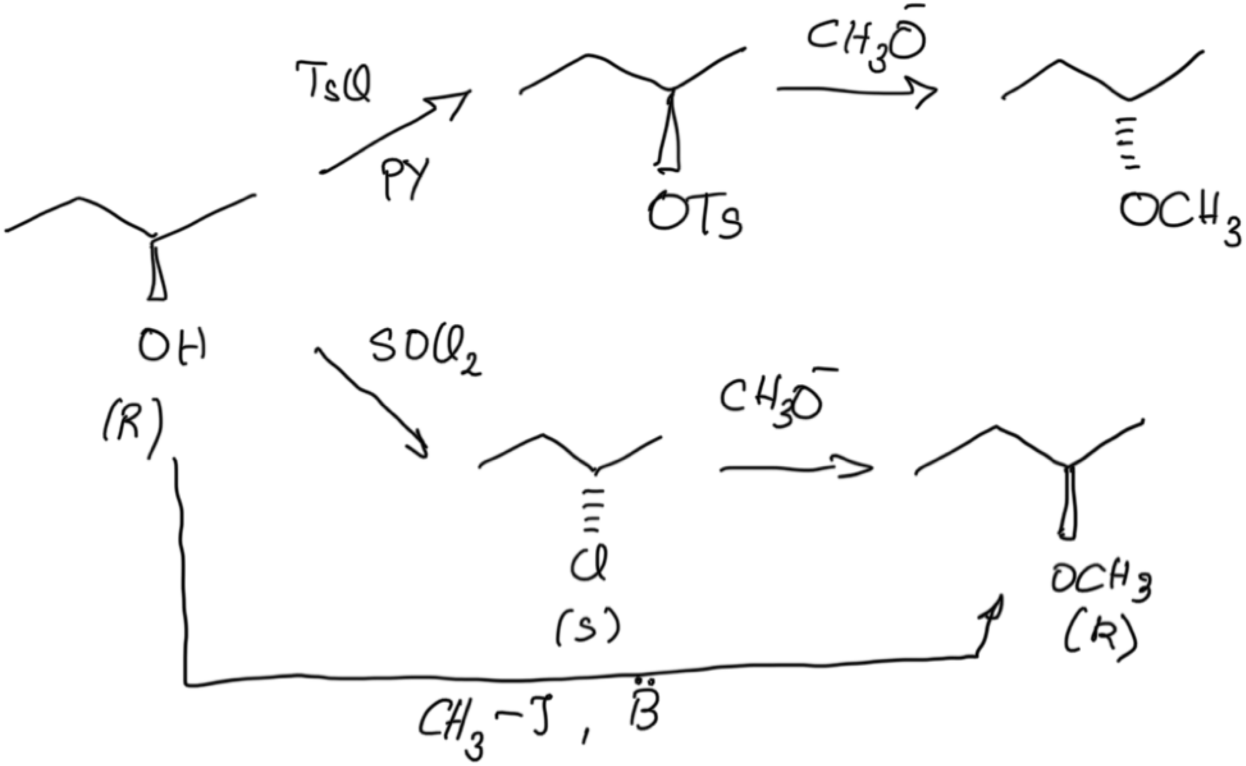
# Tosylate—Another Good Leaving Group



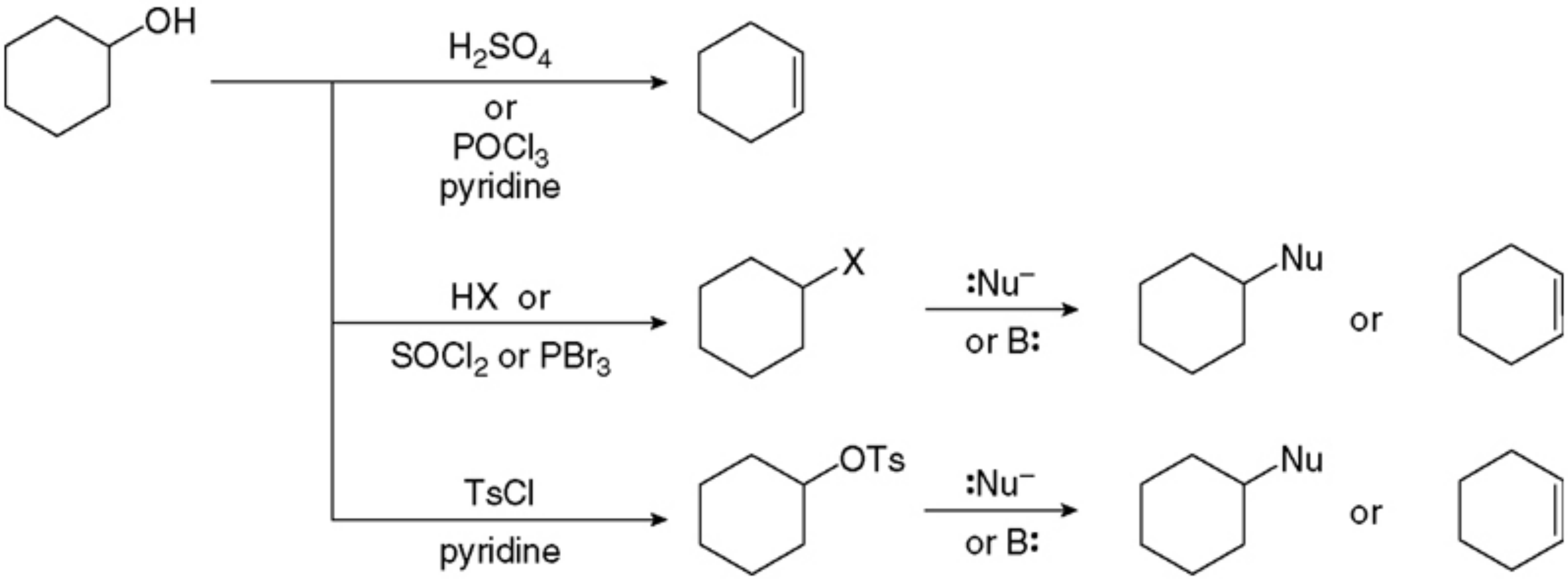
- Tosylate is a good leaving group because its conjugate acid, *p*-toluenesulfonic acid ($CH_3C_6H_4SO_3H$, TsOH) is a strong acid ($pK_a$ = -7).



# Nucleophilic substitutions of alcohols

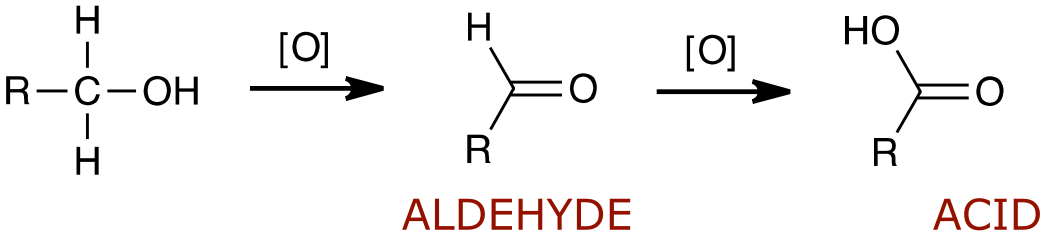


# Nucleophilic substitution and β-elimination reactions of alcohols

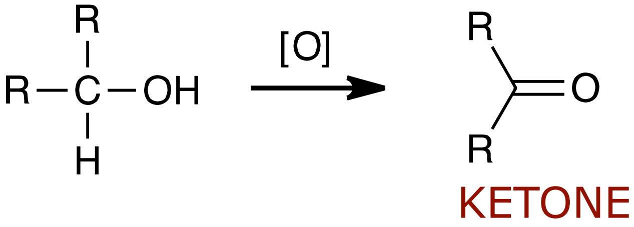


# Oxidation of Alcohols

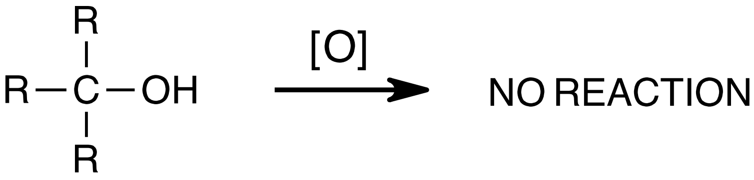
1° ALCOHOL



2° ALCOHOL

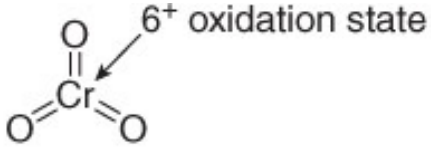


3° ALCOHOL



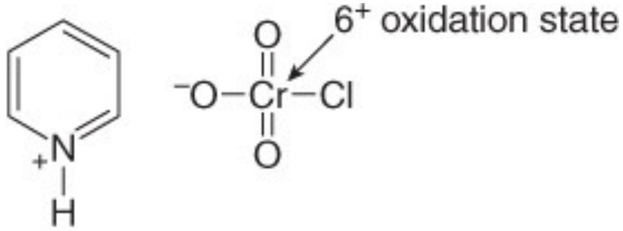
# Oxidation of Alcohols

- The oxidation of alcohols to carbonyl compounds is typically carried out with Cr(VI) oxidants, which are reduced to Cr(III) products.
- $CrO_3$, $Na_2Cr_2O_7$, and $K_2Cr_2O_7$ are strong, nonselective oxidants used in aqueous acid ($H_2SO_4$ + $H_2O$).
- PCC is soluble in $CH_2Cl_2$ (dichloromethane) and can be used without strong acid present, making it a more selective, milder oxidant.



chromium(VI) oxide

**$CrO_3$**



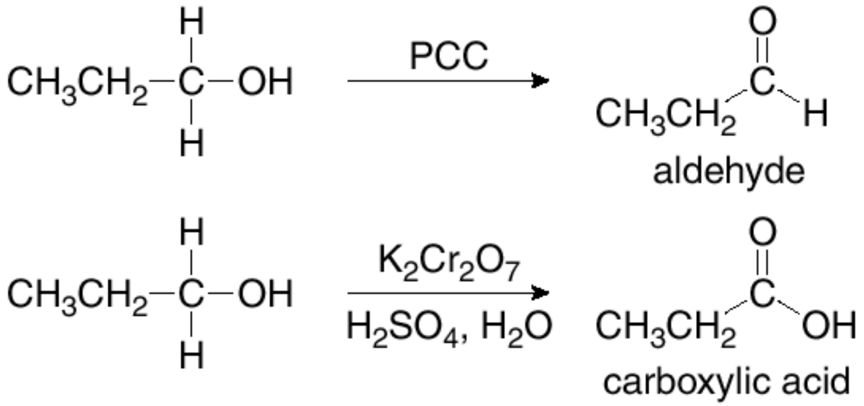
pyridinium chlorochromate

**PCC**

# Oxidation of Alcohols

- 1° Alcohols are oxidized to aldehydes (RCHO) under mild reaction conditions—using PCC in $CH_2Cl_2$.
- 1° Alcohols are oxidized to carboxylic acids (RCOOH) under harsher reaction conditions: $Na_2Cr_2O_7$, $K_2Cr_2O_7$, or $CrO_3$ in the presence of $H_2O$ and $H_2SO_4$.

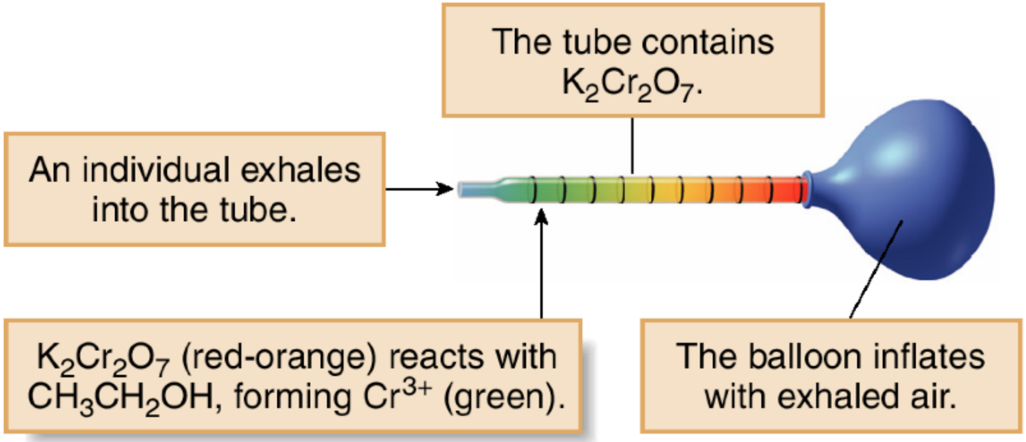
**1° Alcohols**



# The Alcohol Test

- The oxidation of $CH_3CH_2OH$ with $K_2Cr_2O_7$ to form $CH_3COOH$ and $Cr^{3+}$ was the first available method for the routine testing of alcohol concentration in exhaled air. Some consumer products for alcohol screening are still based on this technology.

**Schematic of an alcohol testing device**



The tube contains $K_2Cr_2O_7$.

An individual exhales into the tube.

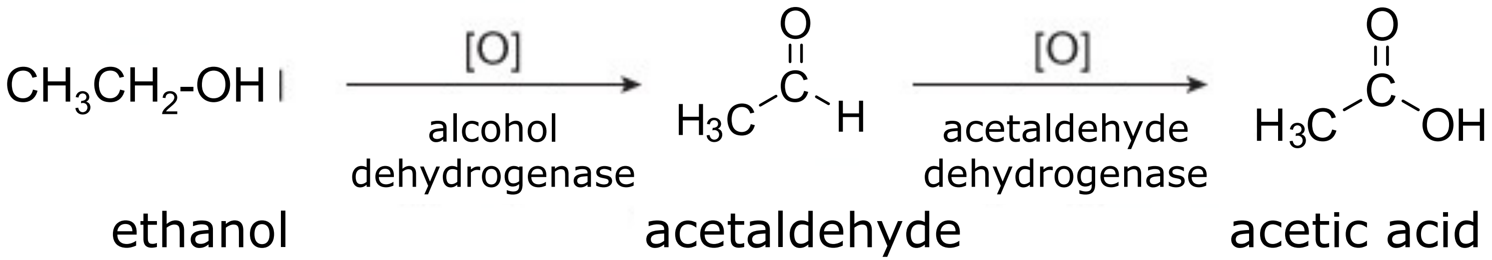
$K_2Cr_2O_7$ (red-orange) reacts with $CH_3CH_2OH$, forming $Cr^{3+}$ (green).

The balloon inflates with exhaled air.

---

**Consumer product**

# Ethanol Metabolism

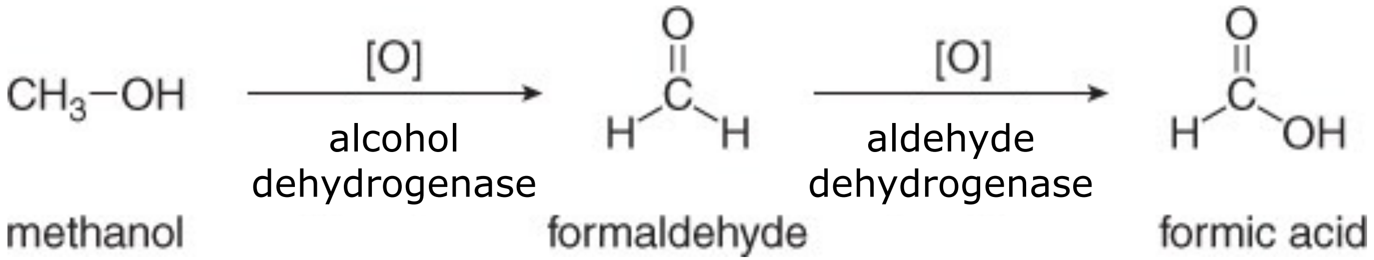


$$CH_3CH_2\text{-}OH \xrightarrow[\text{alcohol dehydrogenase}]{[O]} H_3C\text{-}C(=O)\text{-}H \xrightarrow[\text{acetaldehyde dehydrogenase}]{[O]} H_3C\text{-}C(=O)\text{-}OH$$

ethanol

acetaldehyde

acetic acid



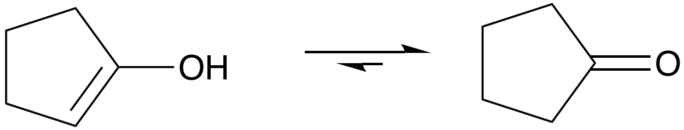
$$CH_3\text{-}OH \xrightarrow[\text{alcohol dehydrogenase}]{[O]} H\text{-}C(=O)\text{-}H \xrightarrow[\text{aldehyde dehydrogenase}]{[O]} H\text{-}C(=O)\text{-}OH$$

methanol

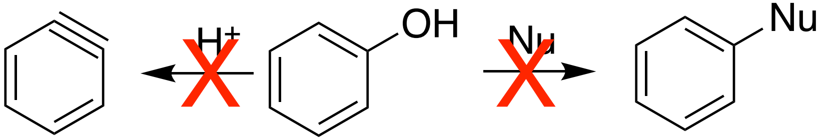
formaldehyde

formic acid

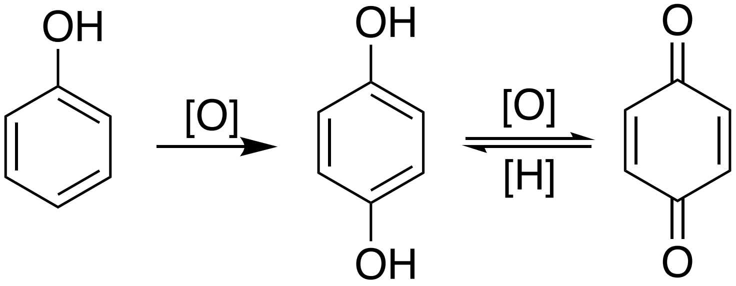
# Phenols and Enols



Enols only exist in equilibrium with the more stable carbonyl compounds



Phenols do not give nucleophilic substitution nor elimination



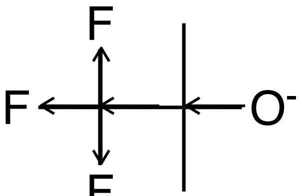
hydroquinone quinone

Phenol is oxidized by strong oxidizing agents. Hydroquinone is a common antioxidant

# Acidity of Alcohols an Phenols

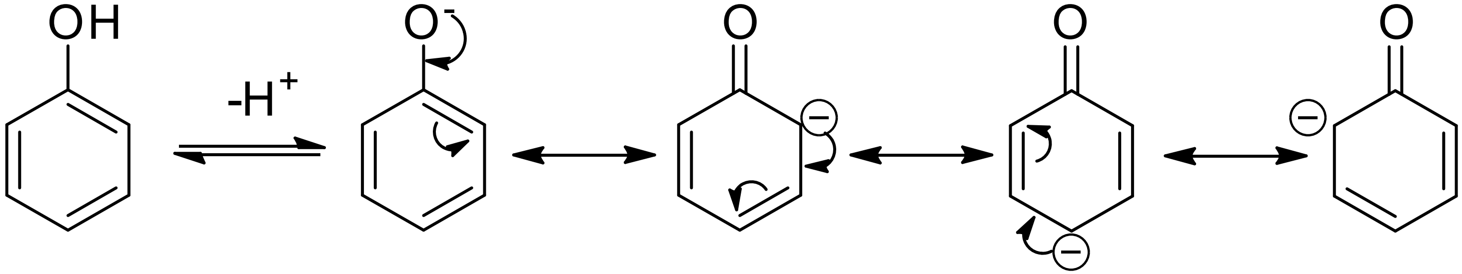
| Compound | $pK_a$ |
|---|---|
| $CH_3CH_2OH$ | 16.0 |
| $CF_3CH_2OH$ | 12.4 |
| $C_6H_5OH$ | 9.9 |
| $p\text{-}NH_2C_6H_4OH$ | 10.5 |
| $p\text{-}NO_2C_6H_4OH$ | 7.2 |

## $CF_3CH_2O^-$: Inductively stabilized



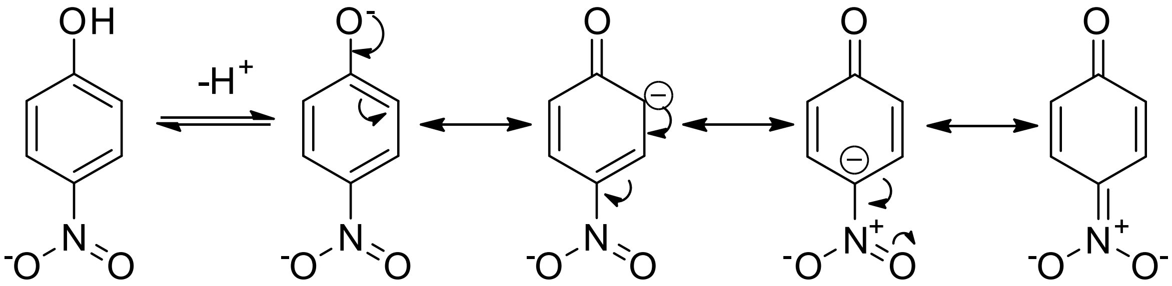
polarization of the C-F bond is transmitted along σ bonds and the negative charge is dispersed on several atoms

## $C_6H_5O^-$: Resonance stabilized

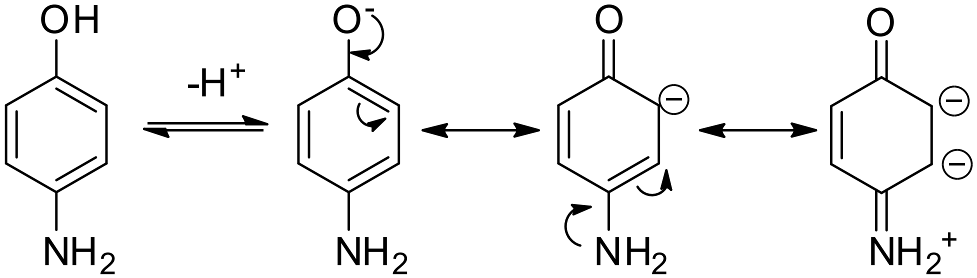


the negative charge is delocalized on the o- and p- positions of the aromatic ring

# Substituent effects on acidity of phenols



Stabilized by delocalization



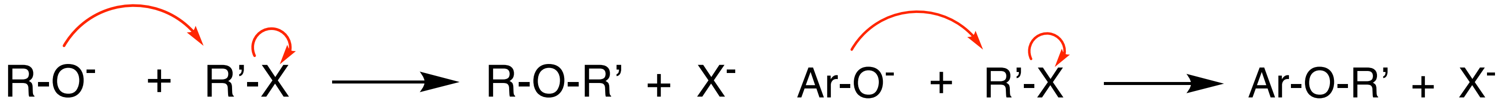
Destabilized by delocalization

# Reactions of Alcohols
# OH as Nucleophile

- Alcohols (R-OH) are weak nucleophiles; alcoxides ($R\text{-}O^-$) are strong nucleophiles.

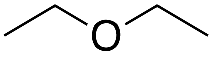
- Phenols (Ar-OH) and phenoxides ($Ar\text{-}O^-$) are weaker nucleophiles than alcohols and alcoxides, respectively, because the Oxygen lone pair is delocalized on the ring.

- Alcohols and phenols can be alkylated with alkyl halides in basic medium giving alkyl and aryl ethers.

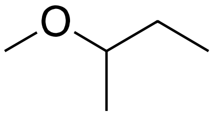


# Nomenclature of Ethers

- Common names:



diethyl ether

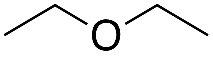


s-butyl methyl ether

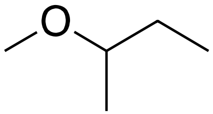
tetrahydrofuran

**THF**

- IUPAC names:



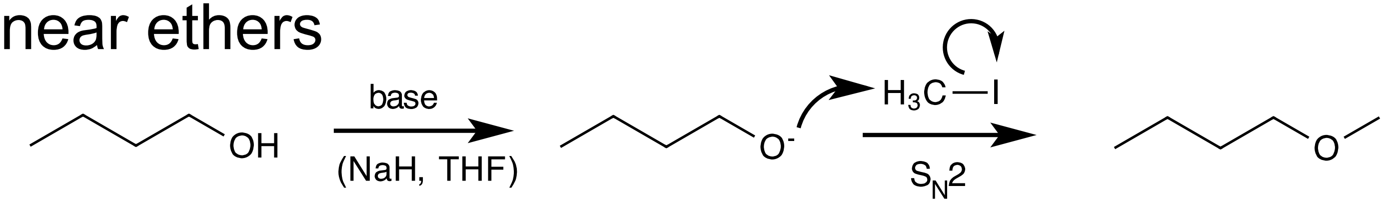
ethoxyethane



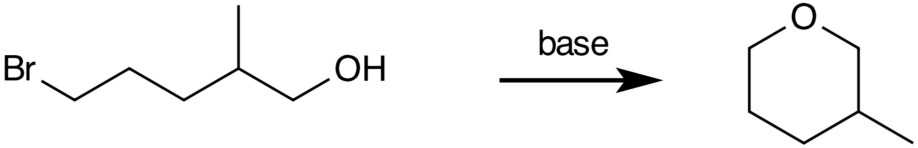
2-methoxybutane

# Preparation of Ethers
# Williamson synthesis

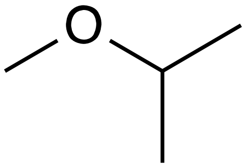
## Linear ethers

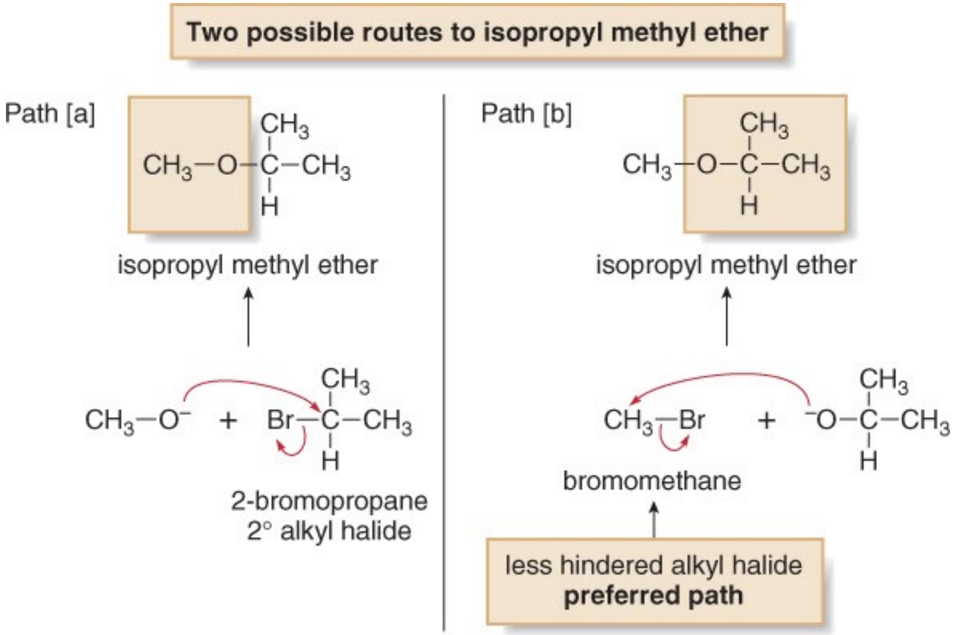


## Cyclic ethers



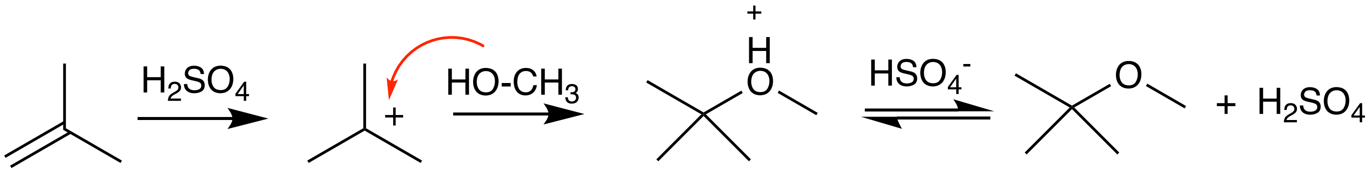
# Preparation of Ethers
# Williamson synthesis



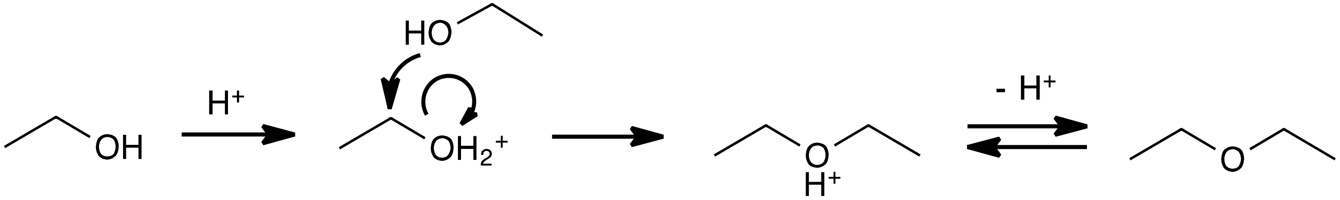


# Preparation of Ethers

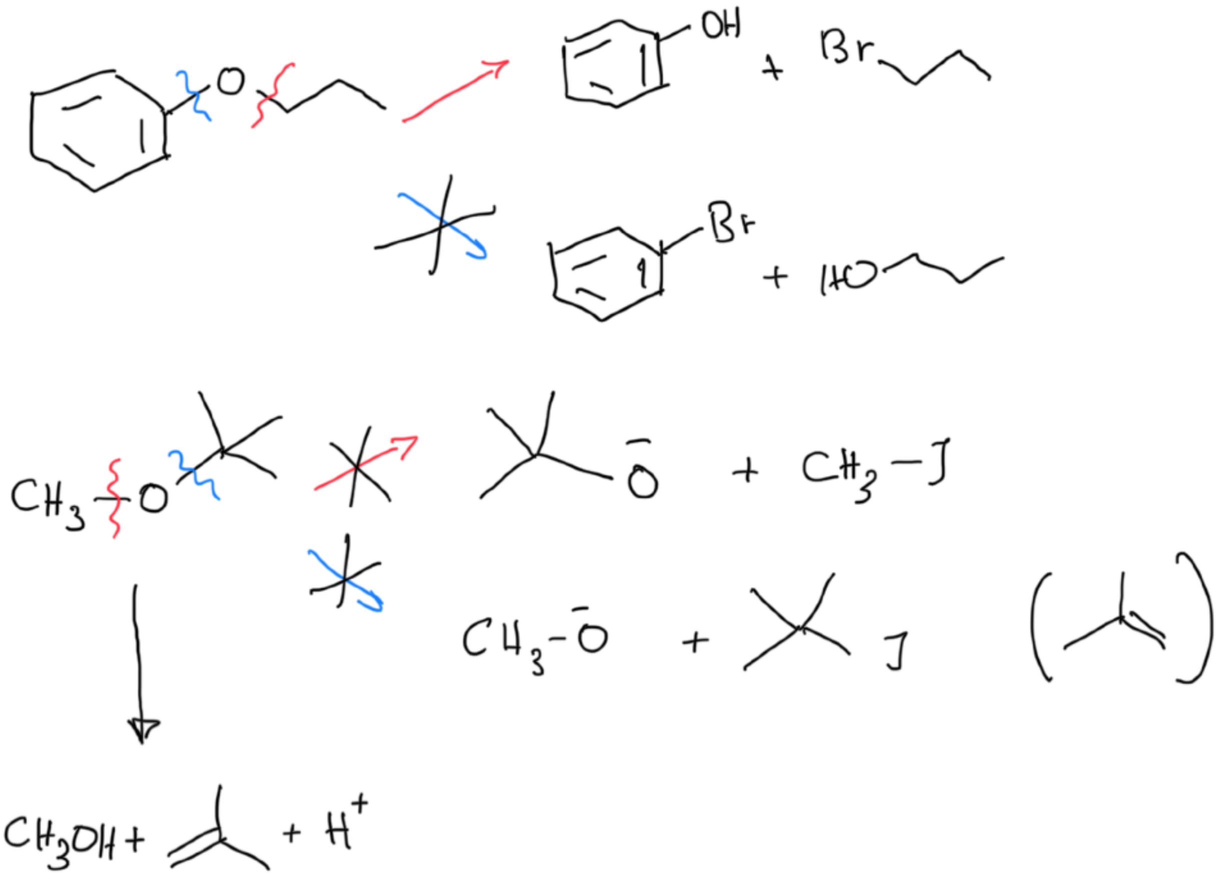
## FROM ALKENES



## FROM ALCOHOLS (for symmetrical ethers)



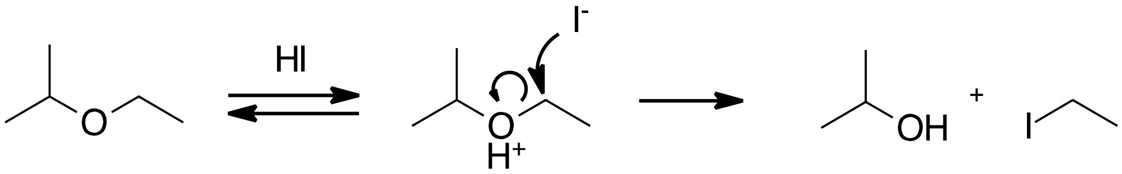
# Preparation of Ethers
# Williamson synthesis



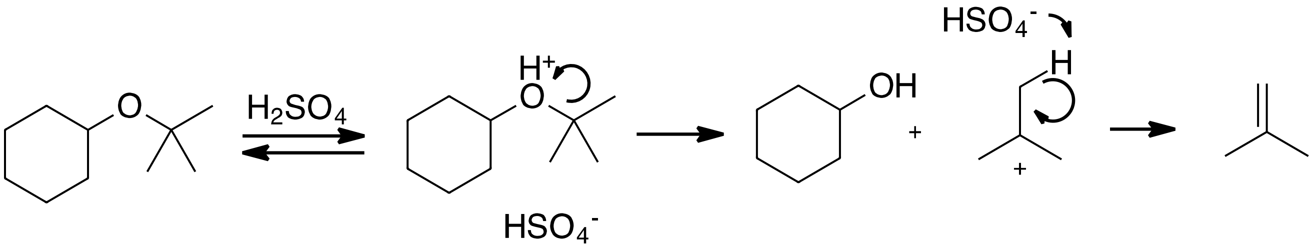
# Reaction of Ethers with Strong Acid

- The ether bond is cleaved with strong acids to give an alcohol and a halide or an alkene

$S_N2$



$S_N1/E1$



# Structure of Epoxides

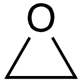
- Epoxides are ethers having the oxygen atom in a three-membered ring. Epoxides are also called oxiranes.

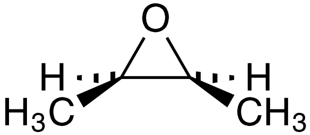
**epoxide** or **oxirane**

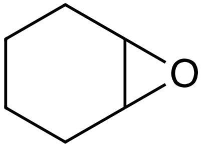
An epoxide is a special type of ether.

- The C—O—C bond angle for an epoxide must be 60°, a considerable deviation from the tetrahedral bond angle of 109.5°. Thus, epoxides have angle strain, making them more reactive than other ethers.

# Nomenclature of Epoxides



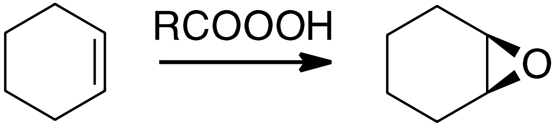


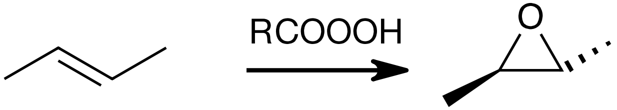


| | | | |
|---|---|---|---|
| 1. IUPAC | oxirane | cis-2,3-dimethyloxirane | 7-Oxabicyclo [4.1.0]heptane |
| 2. as alkene oxides | ethene oxide | cis-2-butene oxide | cyclohexene oxide |
| 3. as epoxyalkanes | epoxyethane | cis-2,3-epoxybutane | 1,2-epoxycyclohexane |

# Preparation of Epoxides

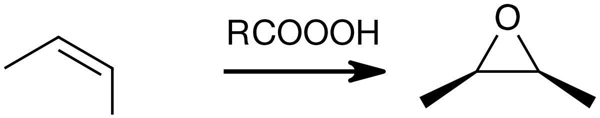
## 1. epoxidation of alkenes





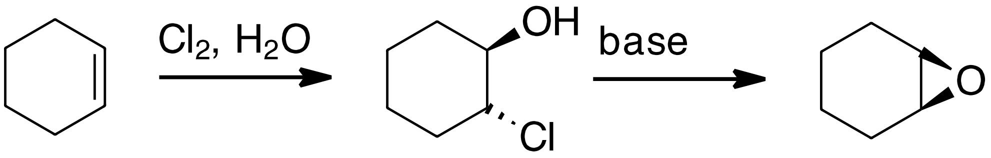
*trans*-2-butene *trans*-1,2-dimethyloxirane

epoxidation is stereoselective

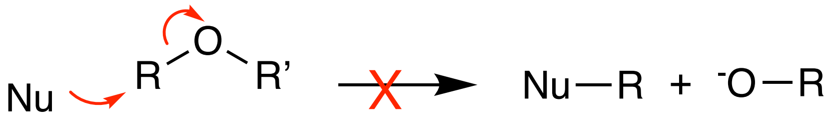


*cis*-2-butene *cis*-1,2-dimethyloxirane

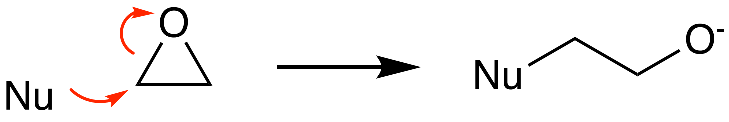
## 2. cyclization of halohydrins



# Reactions of Epoxides



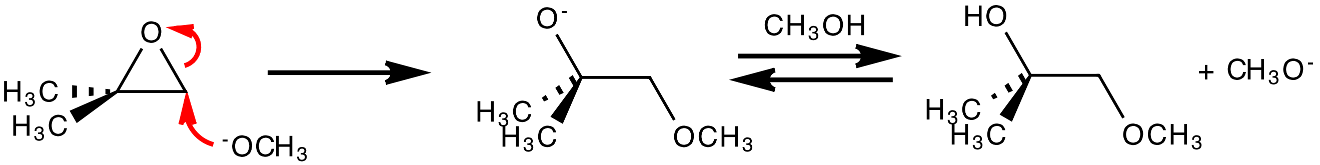
Ethers do not react with nucleophiles



strain is released

Epoxides are very reactive with nucleophiles

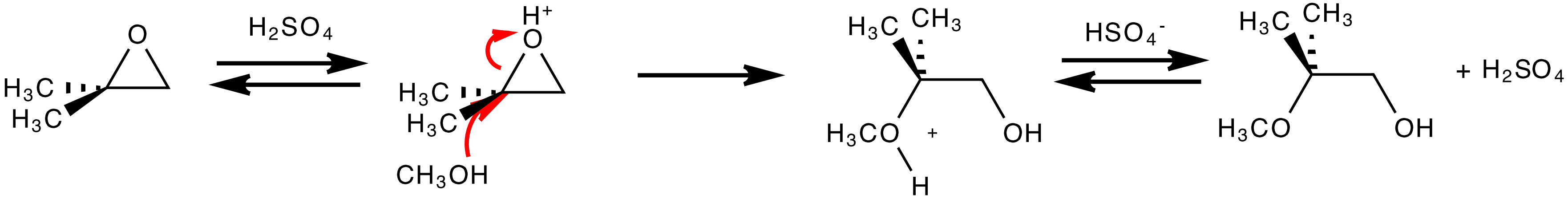
Nucleophilic attack opens the strained three-membered ring with an $S_N2$ mechanism, making it a favourable process even with a poor leaving group.



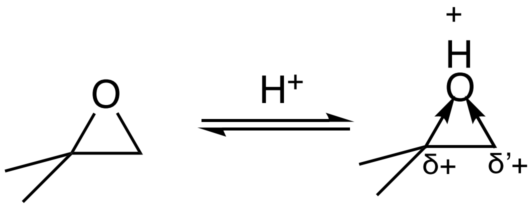
Backside attack on the less substituted carbon: steric control

# Reactions of Epoxides

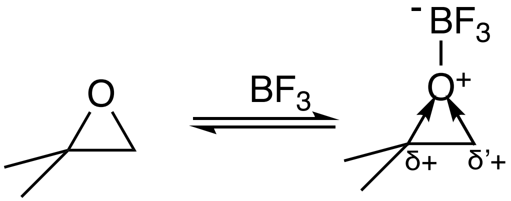
Acids catalyse epoxide ring opening by protonating the oxygen:



Backside attack on the
more substituted carbon:
electronic control

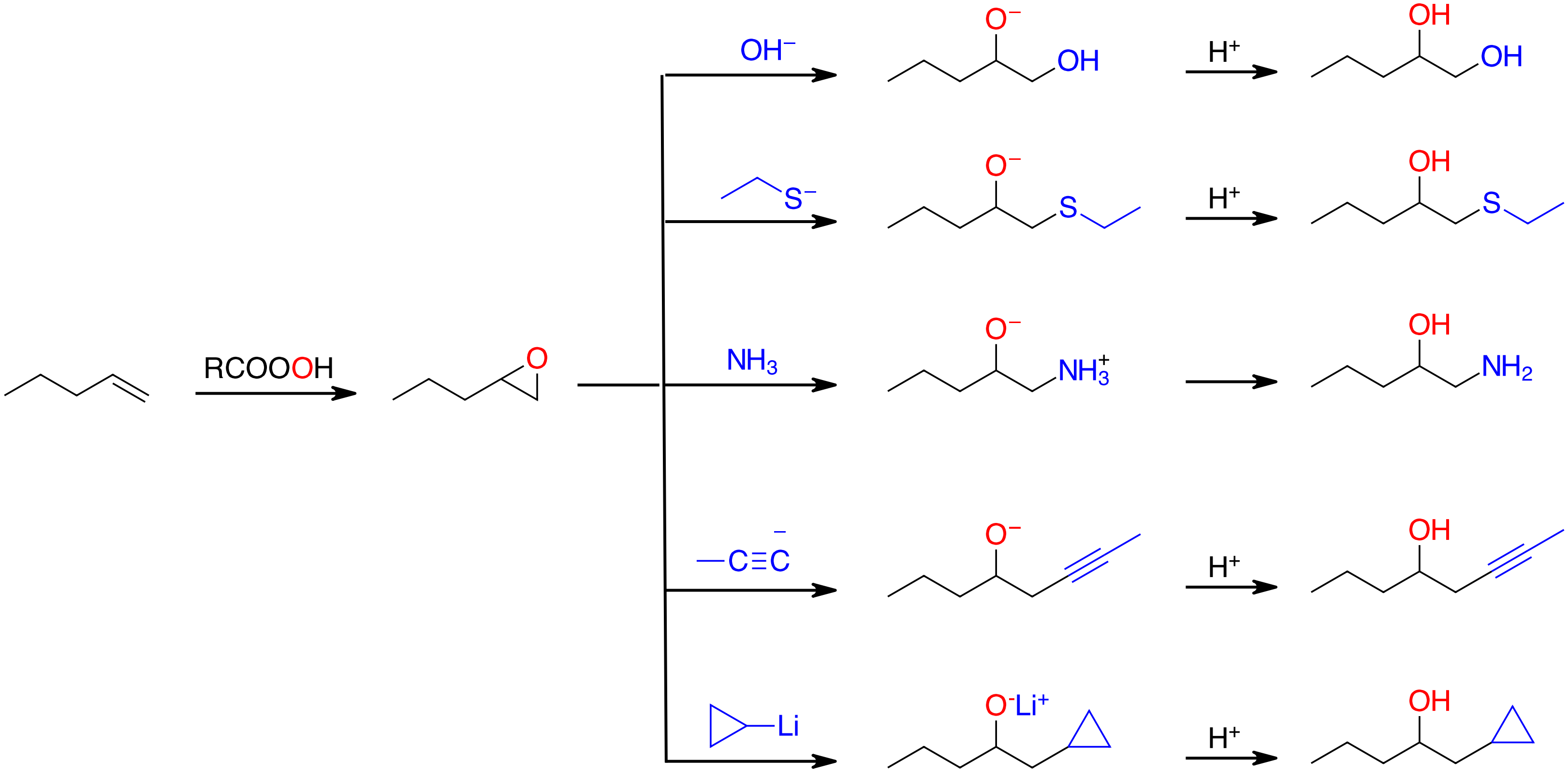


also with
Lewis acids



δ+ > δ′+ : the partial charge is higher on the more substituted carbon

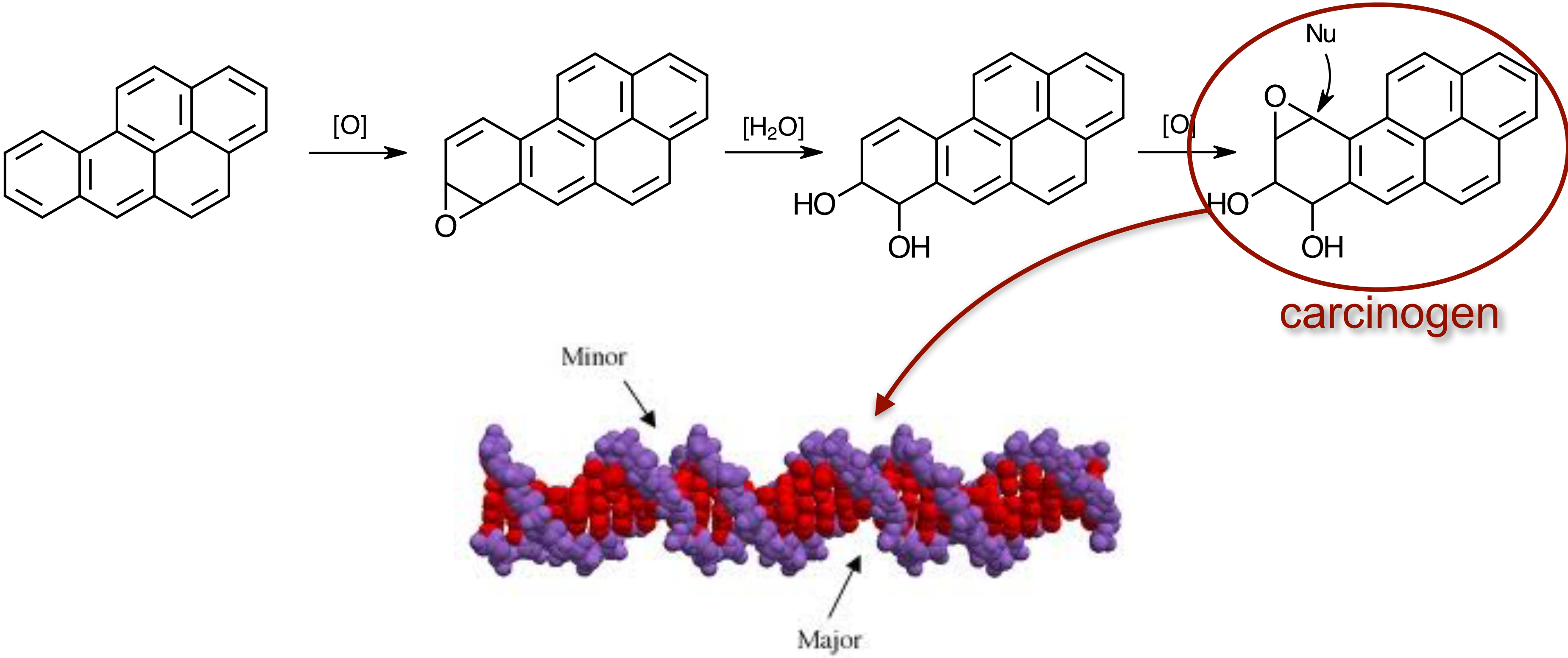
# Epoxides in Organic Synthesis



epoxides react with a variety of nucleophiles

# Reactions of Epoxides

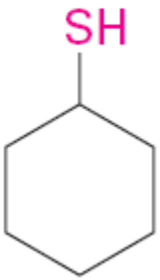
- When polyaromatic hydrocarbons are inhaled or ingested, they are oxidized in the liver to species that often contain a highly reactive epoxide ring.
- The strained three-membered ring reacts readily with biological nucleophiles such as DNA or enzymes, leading to ring-opened products that often disrupt cell function, causing cancer or cell death.



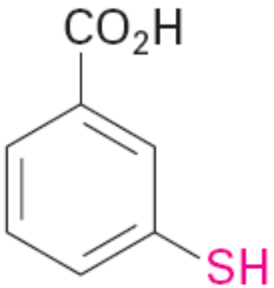
# Thiols and Sulfides: Structure and Nomenclature

$CH_3CH_2SH$

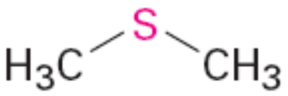
ethanethiol



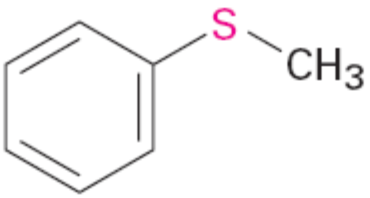
ciclohexanethiol



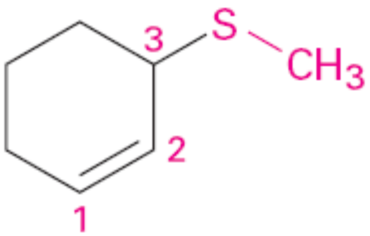
3-mercapto benzoic acid



dimethylsulfide

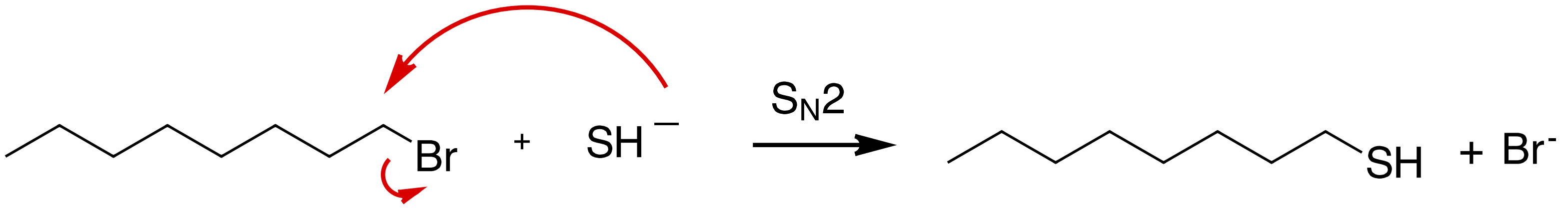


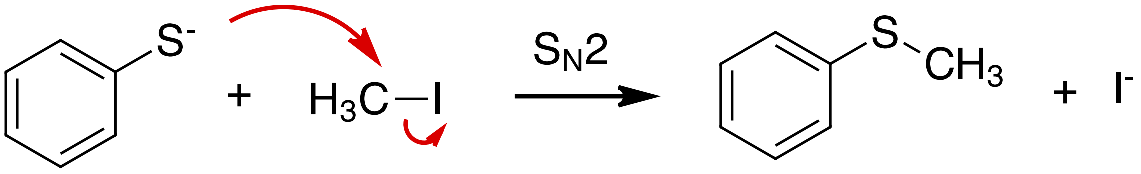
methyl phenyl sulfide



3-(methylmercapto) cyclohexene

# Thiols and Sulfides: Synthesis

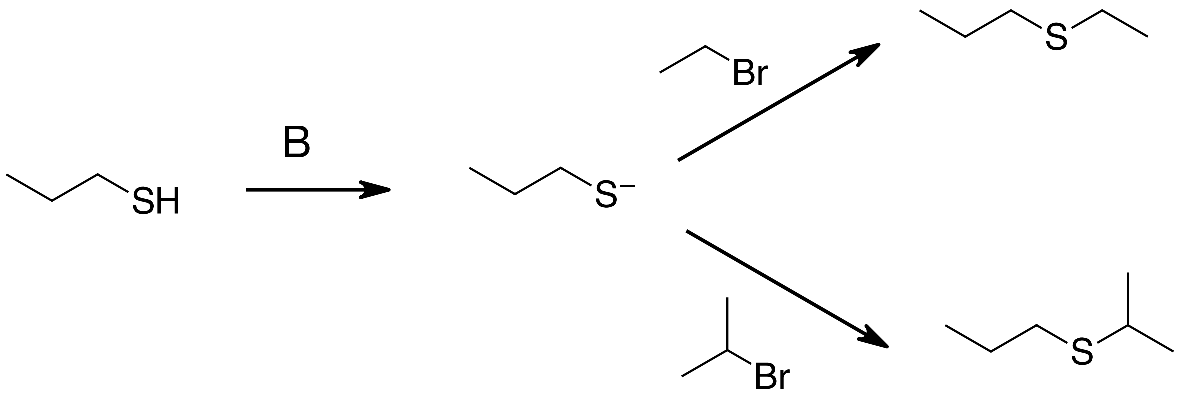




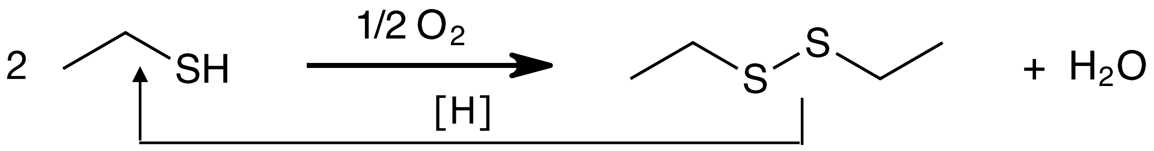
# Thiols and Sulfides: Acidity

| | pKa |
|---|---|
| $Et\text{-}OH + H_2O = Et\text{-}O^- + H_3O^+$ | 16.0 |
| $Et\text{-}SH + H_2O = Et\text{-}S^- + H_3O^+$ | 10.6 |
| $Ph\text{-}OH + H_2O = Ph\text{-}O^- + H_3O^+$ | 10.0 |
| $Ph\text{-}SH + H_2O = Ph\text{-}S^- + H_3O^+$ | 6.6 |

Thiolate ions are excellent nucleophiles and react ($S_N2$) with primary and secondary halides without elimination.

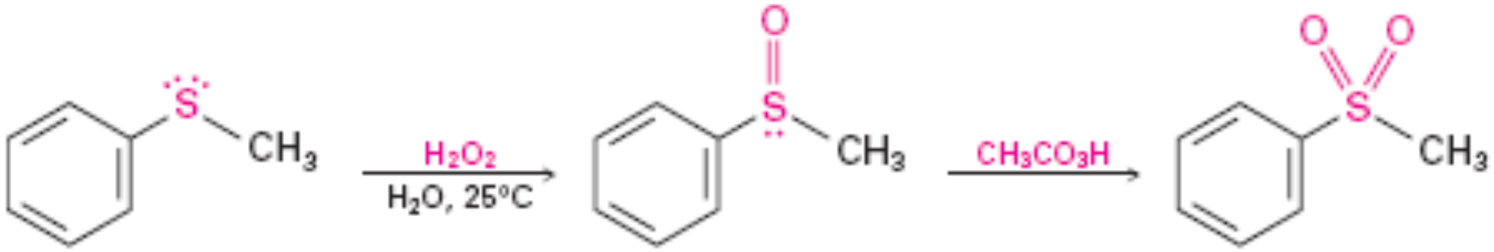


# Thiols and Sulfides: Oxidation



thiol

disulfide

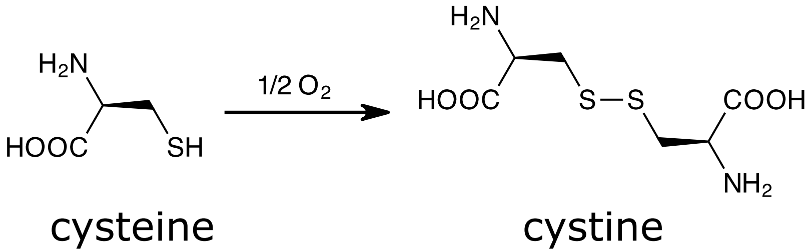


sulfide

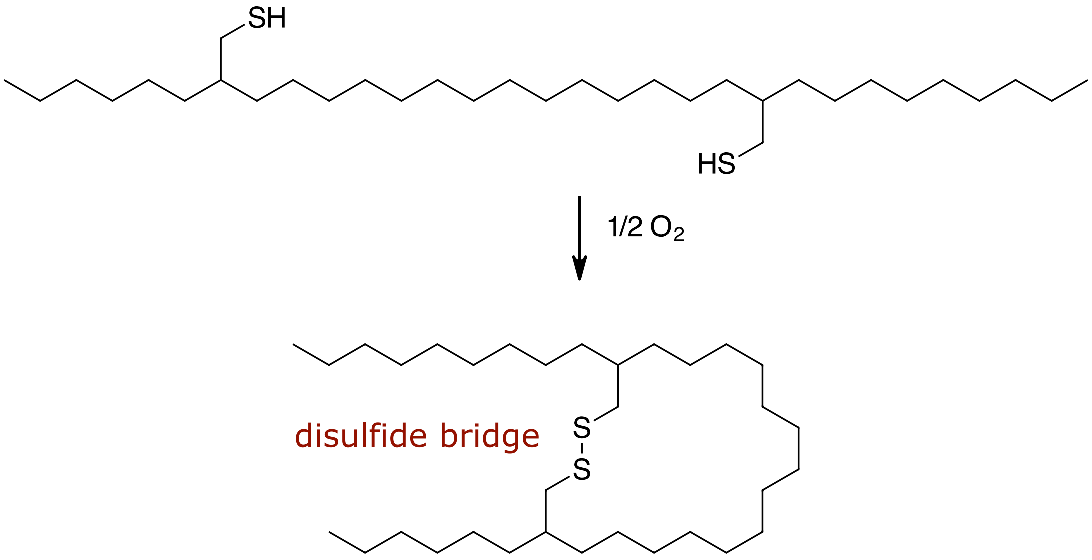
sulfoxide

sulfone

# Thiol Oxidation in Nature



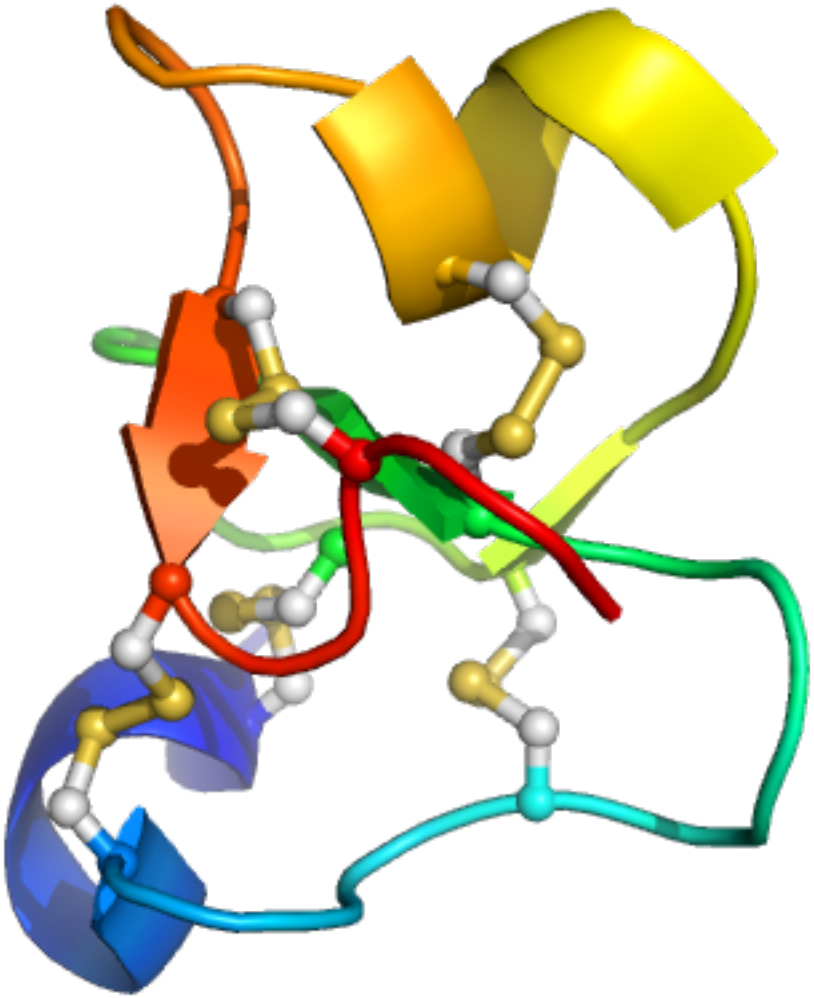
## Protein Folding:



native protein from ribosomal synthesis

folded, functional protein

# Ponti Disolfuro nelle Proteine



modello 3D